Therapeutic Class Overview
Colony Stimulating Factors

Therapeutic Class Overview/Summary:
This review will focus on the granulocyte colony stimulating factors (G-CSFs) and granulocyte-macrophage colony stimulating factors (GM-CSFs).[1-5] Colony-stimulating factors (CSFs) fall under the naturally occurring glycoprotein cytokines, one of the main groups of immunomodulators.[6] In general, these proteins are vital to the proliferation and differentiation of hematopoietic progenitor cells.[6-8] The G-CSFs commercially available in the United States include pegfilgrastim (Neulasta®), filgrastim (Neupogen®), filgrastim-sndz (Zarxio®), and tbo-filgrastim (Granix®). While filgrastim-sndz and tbo-filgrastim are the same recombinant human G-CSF as filgrastim, only filgrastim-sndz is considered a biosimilar drug as it was approved through the biosimilar pathway. At the time tbo-filgrastim was approved, a regulatory pathway for biosimilar drugs had not yet been established in the United States and tbo-filgrastim was filed under its own Biologic License Application.[9] Only one GM-CSF is currently available, sargramostim (Leukine). These agents are Food and Drug Administration (FDA)-approved for a variety of conditions relating to neutropenia or for the collection of hematopoietic progenitor cells for collection by leukapheresis.[1-5] Due to the pathway taken, tbo-filgrastim does not share all of the same indications as filgrastim and these two products are not interchangeable. It is important to note that although filgrastim-sndz is a biosimilar product, and it was approved with all the same indications as filgrastim at the time, filgrastim has since received FDA-approval for an additional indication that filgrastim-sndz does not have, to increase survival in patients with acute exposure to myelosuppressive doses of radiation.[1-3]A complete list of indications for each agent can be found in Table 1. Differences among dosing schedules also exist between the agents. Pegfilgrastim is administered at a fixed dose (6 mg subcutaneously once per chemotherapy cycle), while both filgrastim, filgrastim-sndz, tbo-filgrastim, and sargramostim are dosed based on patient's body weight and are administered daily.[1-5]

The G-CSFs are generally used in patients with cancer to reduce the incidence of adverse events associated with chemotherapy, such as febrile neutropenia, infections and delayed neutrophil recovery time. Neutrophils are the body's defense system against infection and play a key role in the process of acute inflammation.[10] Chemotherapy and radiation can affect neutrophil function as well as decrease the production of neutrophils in the bone marrow. When the absolute neutrophil count (ANC) falls below 1,500 cells/µL, this is defined as neutropenia. Patients who have severe neutropenia (ANC <500 cells/µL) are at high risk for infection.[10] Endogenous G-CSF is a growth factor produced by monocytes, fibroblasts and endothelial cells that acts upon the bone marrow to increase the production of neutrophils. In addition to increasing neutrophil production, G-CSF also enhances phagocytic and cytotoxic actions of mature neutrophils.[1,2] Filgrastim, tbo-filgrastim, filgrastim-sndz and pegfilgrastim are produced by recombinant deoxyribonucleic acid (DNA) technology via the insertion of the human G-CSF gene into *Escherichia coli* (*E coli*) bacteria.[1-3,5] Pegfilgrastim, a long-acting formulation of filgrastim, is produced by conjugating filgrastim with polyethylene glycol, thereby increasing the molecular weight and delaying kidney excretion.[3]

GM-CSF is primarily used to accelerate myeloid recovery in oncology patients following myelosuppressive treatment regimens. Endogenous GM-CSF is predominantly found in T lymphocytes, monocytes, macrophages, fibroblasts and endothelial cells.[6] In addition to increasing the production of neutrophils, GM-CSF also increases other white blood cells including monocytes, macrophages and eosinophils in the bone marrow as well as promoting their function. Like the G-CSFs, sargramostim is also produced utilizing recombinant DNA technology; however it is derived in yeast (*Saccharomyces cerevisiae*) expression system rather than from *E coli* bacteria.[4]

Based on current guidelines regarding the general use of CSFs such as the National Comprehensive Cancer Network (NCCN) Myeloid Growth Factors Clinical Practice Guideline in Oncology and the American Society of Clinical Oncology (ASCO) 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors, both recognize the importance of preventing and limiting the duration of febrile

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neutropenia. Similarly, both guidelines recommend primary prophylaxis with a CSF when the risk of febrile neutropenia is >20%. In addition, they recommend that the therapeutic use of a CSF be considered only when a patient with febrile neutropenia is at high risk of infection-related complications based on prognostic factors.[11,12] There is currently no general consensus among the guidelines regarding the specific CSFs within the class. The NCCN states that when choosing an agent for the treatment of prophylaxis of febrile neutropenia, filgrastim and pegfilgrastim are considered to have stronger data to support their use compared to sargramostim.[11,13] The European Organization for Research and Treatment of Cancer recommends the use of filgrastim and pegfilgrastim while stating that there is some evidence showing G-CSF and GM-CSF are comparable in efficacy.[14] The ASCO state that due to the lack of information, no recommendation can be made with regards to the equivalency of the two G-CSFs.[12]

Table 1. Current Medications Available in the Therapeutic Class[1-5,15-17]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Filgrastim (Neupogen®)	To decrease the incidence of infection associated with severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies; To reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy for acute myeloid leukemia; To reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation; To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; To reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia†; To increase survival in patients acutely exposed to myelosuppressive doses of radiation.	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL	a *
Filgrastim-sndz (Zarxio®*)	To decrease the incidence of infection associated with severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies; To reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy for acute myeloid leukemia; To reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation; To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; To reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL	a *

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Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	neutropenia, cyclic neutropenia, or idiopathic neutropenia†.		
Pegfilgrastim (Neulasta®)	To decrease the incidence of infection associated with severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies.	Prefilled Syringe: 6 mg/0.6 mL	-
Sargramostim (Leukine®)	Allogeneic or autologous bone marrow transplantation in which engraftment is delayed or has failed; To reduce the time to neutrophil recovery and the duration of fever following induction chemotherapy for acute myeloid leukemia‡; To accelerate myeloid recover in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation; To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.	Vial (powder for reconstitution): 250 µg Vial (solution) 500 µg/1 mL	-
Tbo-Filgrastim (Granix®)	To decrease the incidence of infection associated with severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies.		-

*Zarxio® is a bio-similar medication and interchangeable with the reference drug Neupogen®.
†Indicated for chronic use.
‡Safety and efficacy has not been established in patients <55 years of age.

Evidence-based Medicine

- The safety and efficacy of the granulocyte and granulocyte-macrophage colony stimulating factors have been evaluated in several clinical trials, however, there are few trials that compare G-CSFs to GM-CSFs.[18-53]
- Two retrospective trials evaluated the differences in efficacy between filgrastim and pegfilgrastim in patients with nonmyeloid malignancies who underwent chemotherapy. Pegfilgrastim was associated with fewer episodes of febrile neutropenia as well as fewer hospitalizations for febrile neutropenia compared to filgrastim[18,19]
- There were no significant differences between treatment groups in the duration of severe neutropenia and the depth of ANC nadir in all cycles when single-dose pegfilgrastim is compared to daily filgrastim.[21]
- When comparing filgrastim to sargramostim, there was no significant difference among the treatment groups in the mean number of days to reach an ANC 500 cells/µL (P=0.32); however, the mean number of days to reach an ANC 1,000 and 1,500 cells/µL was significantly lower in the filgrastim group compared to the sargramostim group (P=0.009 and P=0.0001, respectively).[22]
- A Cochrane review of 13 randomized, placebo-controlled trials was performed to evaluate the efficacy and safety of filgrastim, lenograstim (not available in the United States) or sargramostim compared to placebo in patients who were receiving nonmyeloablative chemotherapy for malignant lymphomas. Sensitivity analyses that were performed in this review concluded that there were no differences between G-CSF and GM-CSF in their effects on overall survival, freedom from treatment failure and risk reduction in incidence of neutropenia or febrile neutropenia.[24]
- Additional studies generally suggest that filgrastim provides statistically significant efficacy compared to sargramostim, however there is data in several trails saying there is no difference or that sargramostim is more effective.[37,44,50]

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- The FDA-approval of tbo-filgrastim was evaluated in a single multi-center, placebo- and active-controlled, randomized control trial that evaluated patients with breast cancer. Patients received tbo-filgrastim, filgrastim, or placebo for cycle one. For cycle two to four, the patients that received placebo were switched to tbo-filgrastim. Doses were 5µg/kg daily for both active treatment groups for all cycles. The primary efficacy endpoint was duration of severe neutropenia in cycle one. When compared to placebo, tbo-filgrastim was provided a statistically significant improvement in duration of severe neutropenia (no P value reported). When compared to filgrastim, tbo-filgrastim was considered equivalent with a least square mean difference of 0.028 (95% CI, -0.262 to 0.325). Secondary endpoints showed no differences between tbo-filgrastim and filgrastim during any cycle or overall.[38]
    - Two additional studies published showed similar results but in patients with aggressive non-Hodgkin's lymphoma and small cell or non-small cell lung cancer.[39,40]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Primary prophylaxis with a CSF is recommended when the risk of febrile neutropenia is greater than 20%[11,12]
    - Therapeutic use of a CSF be considered only when a patient with febrile neutropenia is at high risk of infection-related complications based on prognostic factors.[11,12]
    - There is currently no general consensus among the guidelines regarding the specific CSFs within the class.
        - The National Comprehensive Cancer Network filgrastim and pegfilgrastim are considered to have stronger data to support their use compared to sargramostim.[11,13]
        - The European Organization for Research and Treatment of Cancer recommends the use of filgrastim and pegfilgrastim while stating that there is some evidence showing G-CSF and GM-CSF are comparable in efficacy.[14]
        - The American Society of Clinical Oncology states that due to the lack of information, no recommendation can be made with regards to the equivalency of the two G-CSFs.[12]

- Other Key Facts:
    - Filgrastim and filgrastim-sndz are approved for use in pediatric patients (no age restriction)[1,2]
    - Dosing for pegfilgrastim is less frequent (once per chemotherapy cycle) than other CSFs (daily for five to 12 days) due to its long half-life.[1-5]
    - All agents except sargramostim are available as prefilled syringes. Pegfilgrastim and tbo-filgrastim are not available in as a single-use vial.[1-5]
    - Although filgrastim-sndz is a biosimilar agent, it does not share the indication of increasing survival in patients acutely exposed to myelosuppressive doses of radiation with its reference product, filgrastim.[1,2]

References

1. Neupogen® [package insert]. Thousand Oaks (CA): Amgen Inc.; 2015 Mar.
2. Zarxio® [package insert]. Princeton (NJ): Sandoz Inc.; 2015 Mar.
3. Neulasta® [package insert]. Thousand Oaks (CA): Amgen Inc.; 2014 Dec.
4. Leukine® [package insert]. Bridgewater (NJ): Sanofi-Aventis U.S. LLC; 2013 Apr.
5. Granix® [package insert]. North Wales (PA): Teva Pharmaceuticals USA, Inc.; 2014 Dec.
6. Liles WC. Immunomodulators. In: Mandell GL, Bennett JE, Dolin R, editors. Manell, Bennett, & Dolin: Principles and Practice of Infectious Diseases [monograph on the internet]. 7th ed. Philadelphia: Churchill Livingston: 2009 [cited 2011 Apr 19]. Available from: http://www.mdconsult.com/das/book/body/110770361-5/773675061/1259/315.html#4-u1.0-B0-443-06643-4.50042-8--cesec1_1721.
7. Blood Formation, Coagulation, and Thrombosis agents 20.00, Hematopoietic Agents 20.16. In: McEvoy GK, editor: American Hospital Formulary Service. AHFS drug information 2011 [monograph on the internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2011 [cited 2011 Apr 19]. Available from: http://online.statref.com.
8. Medina PJ, Fausel C. Cancer treatment and chemotherapy. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 7th edition. New York (NY): McGraw-Hill; 2008. p. 2085-119.
9. Pappas AL, Hanna, S. *TBO-filgrastim (granix).* Pharmacy Times (2014) Retrieved Aug, 2015, from http://www.pharmacytimes.com/publications/health-system-edition/2014/march2014/tbo-filgrastim-granix.

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10. Baehner R. Neutrophil functions other than movement. In: Basow DS (Ed). UpToDate [database on internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Apr 19]. Available from: http://www.utdol.com/utd/index.do.
11. The NCCN Myeloid Growth Factors Clinical Practice Guidelines in Oncology (Version 1.2010). Fort Washington (PA): National Comprehensive Cancer Network, Inc. 2011 [accessed 2011 Apr 17]. Available from: http://www.nccn.org/index.asp.
12. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006 Jul 1;24(19):3187-205.
13. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 2.2011). Fort Washington (PA): National Comprehensive Cancer Network, Inc. 2011 [accessed 2011 Apr 17]. Available from: http://www.nccn.org/index.asp.
14. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011 Jan;47(1):8-32.
15. Micromedex® Healthcare Series [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. [Cited 2014 Sep]. Available from: http://www.thomsonhc.com/.
16. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2014 Sep]. Available from: http://online.factsandcomparisons.com.
17. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2015 [cited: Aug 4 2015]. Available from: http://www.clinicalpharmacology.com.
18. Almenar D, Mayans J, Juan O, Bueno JM, Lopez JI, Frau A, et al. Pegfilgrastim and daily granulocyte colony-stimulating factor: patterns of use and neutropenia-related outcomes in cancer patients in Spain-results of the LEARN Study. Eur J Cancer Care (Engl). 2009 May;18(3):280-6.
19. Weycker D, Malin J, Kim J, Barron R, Edelsberg J, Kartashov A, et al. Risk of hospitalization for neutropenic complications of chemotherapy in patients with primary solid tumors receiving pegfilgrastim or filgrastim prophylaxis: a retrospective cohort study. Clin Ther. 2009 May;31(5):1069-81.
20. Weycker D, Malin J, Barron R, Edelsberg J, Kartashov A, Oster G. Comparative effectiveness of filgrastim, pegfilgrastim, and sargramostim as prophylaxis against hospitalization for neutropenic complications in patients with cancer receiving chemotherapy. Am J Clin Oncol. 2011 Mar 2 [Epub ahead of print]. doi: 10.1097/COC.0b013e31820dc075.
21. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol. 2002 Feb 1;20(3):727-31.
22. Beveridge RA, Miller JA, Kales AN, et al. A comparison of efficacy of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. Cancer Invest. 1998;16(6):366-73.
23. Beveridge RA, Miller JA, Kales AN, et al. Randomized trial comparing the tolerability of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in cancer patients receiving myelosuppressive chemotherapy. Support Care Cancer. 1997 Jul;5(4):289-98.
24. Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD003189.
25. Heaney ML, Toy EL, Vekeman F, Laliberté F, Dority BL, Perlman D, et al. Comparison of hospitalization risk and associated costs among patients receiving sargramostim, filgrastim, and pegfilgrastim for chemotherapy-induced neutropenia. Cancer. 2009 Oct 15;115(20):4839-48.
26. Nemunaitis J, Rabinowe SN, Singer JW, et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. N Engl J Med. 1991 Jun 20;324(25):1773-8.
27. Lazarus HM, Andersen J, Chen MG, et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for relapsed non-Hodgkin's lymphoma: blood and bone marrow progenitor growth studies. A phase II Eastern Cooperative Oncology Group Trial. Blood. 1991 Aug 1;78(3):830-7.
28. Rabinowe SN, Neuberg D, Bierman PJ, et al. Long-term follow-up of a phase III study of recombinant human granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid malignancies. Blood. 1993 Apr 1;81(7):1903-8.
29. Nemunaitis J, Rosenfeld CS, Ash R, et al. Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. Bone Marrow Transplant. 1995 Jun;15(6):949-54.
30. Bernini JC, Wooley R, Buchanan GR. Low-dose recombinant human granulocyte colony-stimulating factor therapy in children with symptomatic chronic idiopathic neutropenia. J Pediatr. 1996 Oct;129(4):551-8.
31. Welte K, Zeidler C, Reiter A, et al. Differential effects of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor in children with severe congenital neutropenia. Blood. 1990 Mar 1;75(5):1056-63.
32. Grigg A, Solal-Celigny P, Hoskin P, et al. Open-label, randomized study of pegfilgrastim vs daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma. Leuk Lymphoma. 2003 Sep;44(9):1503-8.
33. Holmes FA, Jones SE, O'Shaughnessy J, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. Ann Oncol. 2002 Jun;13(6):903-9.
34. Green MD, Koelbl H, Baselga J, et al. VA randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol. 2003 Jan;14(1):29-35.
35. Vose JM, Crump M, Lazarus H, et al. Randomized, multicenter, open-label study of pegfilgrastim compared to daily filgrastim after chemotherapy for lymphoma. J Clin Oncol. 2003 Feb 1;21(3):514-9.
36. Staber PB, Holub R, Linkesch W, Schmidt H, Neumeister P. Fixed-dose single administration of Pegfilgrastim vs daily Filgrastim in patients with hematological malignancies undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2005 May;35(9):889-93.

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37. Milkovich G, Moleski RJ, Reitan JF, et al. Comparative safety of filgrastim versus sargramostim in patients receiving myelosuppressive chemotherapy. Pharmacotherapy. 2000 Dec;20(12):1432-40.
38. del Giglio A, Eniu A, Ganea-Motan D, Topuzov E, Lubenau H. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer. 2008 Nov 12;8:332. doi: 10.1186/1471-2407-8-332.
39. Engert A, Griskevicius L, Zyuzgin Y, Lubenau H, del Giglio A. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. Leuk Lymphoma. 2009 Mar;50(3):374-9. doi: 10.1080/10428190902756081.
40. Gatzemeier U, Ciuleanu T, Dediu M, Ganea-Motan E, Lubenau H, Del Giglio A. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. J Thorac Oncol. 2009 Jun;4(6):736-40. doi: 10.1097/JTO.0b013e3181a52964.
41. Weisdorf DJ, Verfaillie CM, Davies SM, et al. Hematopoietic growth factors for graft failure after bone marrow transplantation: a randomized trial of granulocyte-macrophage colony-stimulating factor (GM-CSF) vs sequential GM-CSF plus granulocyte-CSF. Blood. 1995 Jun 15;85(12):3452-6.
42. Nemunaitis J, Singer JW, Buckner CD, et al. Use of recombinant human granulocyte-macrophage colony-stimulating factor in graft failure after bone marrow transplantation. Blood. 1990 Jul 1;76(1):245-53.
43. Putkonen M, Rauhala A, Pelliniemi TT, Remes K. Single-dose pegfilgrastim is comparable to daily filgrastim in mobilizing peripheral blood stem cells: a case-matched study in patients with lymphoproliferative malignancies. Ann Hematol. 2009 Jul;88(7):673-80.
44. Martino M, Pratico` G, Messina G, et al. Pegfilgrastim compared to filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. Eur J Haematol. 2006 Nov;77(5):410-5.
45. Martino M, Pratico` G, Messina G, et al. Pegfilgrastim compared to filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. Eur J Haematol. 2006 Nov;77(5):410-5.
46. Castagna L, Bramanti S, Levis A, Michieli MG, Anastasia A, Mazza R, et al. Pegfilgrastim vs filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. Ann Oncol. 2010 Jul;21(7):1482-5.
47. Mathew S, Adel N, Rice RD, Panageas K, Duck ET, Comenzo RL, et al. Retrospective comparison of the effects of filgrastim and pegfilgrastim on the pace of engraftment in auto-SCT patients. Bone Marrow Transplant. 2010 Oct;45(10):1522-7.
48. Samaras P, Buset EM, Siciliano RD, Haile SR, Petrausch U, Mischo A, et al. Equivalence of pegfilgrastim and filgrastim in lymphoma patients treated with BEAM followed by autologous stem cell transplantation. Oncology. 2010;79(1-2):93-7.
49. Samaras P, Blickenstorfer M, Siciliano RD, Haile SR, Buset EM, Petrausch U, et al. Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with melphalan 200 and auto-SCT compared to filgrastim. Ann Hematol. 2011 Jan;90(1):89-94.
50. Jansen J, Thompson EM, Hanks S, et al. Hematopoietic growth factor after autologous peripheral blood transplantation: comparison of G-CSF and GM-CSF. Bone Marrow Transplant. 1999 Jun;23(12):1251-6.
51. Stone RM, Berg DT, George SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. N Engl J Med. 1995 Jun 22;332(25):1671-7.
52. Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood. 1995 Jul 15;86(2):457-62.
53. Büchner T, Hiddemann W, Koenigsmann M, et al. Recombinant human granulocyte-macrophage colony-stimulating factor after chemotherapy in patients with acute myeloid leukemia at higher age or after relapse. Blood. 1991 Sep 1;78(5):1190-7.

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GM-CSF is primarily used to accelerate myeloid recovery in oncology patients following myelosuppressive treatment regimens. Endogenous GM-CSF is predominantly found in T lymphocytes, monocytes, macrophages, fibroblasts and endothelial cells.[6] In addition to increasing the production of neutrophils, GM-CSF also increases other white blood cells including monocytes, macrophages and eosinophils in the bone marrow as well as promoting their function. Like the G-CSFs, sargramostim is also produced utilizing recombinant DNA technology; however it is derived in yeast (*Saccharomyces cerevisiae*) expression system rather than from *E coli* bacteria.[4]

Based on current guidelines regarding the general use of CSFs such as the National Comprehensive Cancer Network (NCCN) Myeloid Growth Factors Clinical Practice Guideline in Oncology and the American Society of Clinical Oncology (ASCO) 2006 Update of Recommendations for the Use of White

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Blood Cell Growth Factors, both recognize the importance of preventing and limiting the duration of febrile neutropenia. Similarly, both guidelines recommend primary prophylaxis with a CSF when the risk of febrile neutropenia is >20%. In addition, they recommend that the therapeutic use of a CSF be considered only when a patient with febrile neutropenia is at high risk of infection-related complications based on prognostic factors.[11,12] There is currently no general consensus among the guidelines regarding the specific CSFs within the class. The NCCN states that when choosing an agent for the treatment of prophylaxis of febrile neutropenia, filgrastim and pegfilgrastim are considered to have stronger data to support their use compared to sargramostim.[11,13] The European Organization for Research and Treatment of Cancer recommends the use of filgrastim and pegfilgrastim while stating that there is some evidence showing G-CSF and GM-CSF are comparable in efficacy.[14] The ASCO state that due to the lack of information, no recommendation can be made with regards to the equivalency of the two G-CSFs.[12]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Filgrastim (Neupogen®)	Granulocyte colony stimulating factor	a *
Filgrastim-sndz (Zarxio®*)	Granulocyte colony stimulating factor	-
Pegfilgrastim (Neulasta®)	Granulocyte colony stimulating factor	-
Sargramostim (Leukine®)	Granulocyte-macrophage colony stimulating factor	-
Tbo-Filgrastim (Granix®)	Granulocyte colony stimulating factor	-

*Zarxio® is a biosimilar to the reference drug Neupogen®.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-5]

Indication	Filgrastim	Filgrastim-sndz	pegfilgrastim	Sargramostim	Tbo-Filgrastim
Allogeneic or autologous bone marrow transplantation in which engraftment is delayed or has failed.				a	
To decrease the incidence of infection associated with severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies.	a	a	a		a
To reduce the time to neutrophil recovery and the duration of fever following induction chemotherapy for acute myeloid leukemia.	a	a		a †	
To reduce the time to neutrophil recovery and the duration of fever following consolidation chemotherapy for acute myeloid leukemia.	a	a			
To reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.	a	a			
To accelerate myeloid recover in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation.				a	
To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.	a	a		a	
To reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or	a *	a *			

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Indication	Filgrastim	Filgrastim-sndz	pegfilgrastim	Sargramostim	Tbo-Filgrastim
idiopathic neutropenia.					
To increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome).	a				

*Indicated for chronic use
†Safety and efficacy has not been established in patients <55 years of age.

Although not Food and Drug Administration (FDA) approved, filgrastim has been used for the treatment of graft failure after bone marrow transplantation, neutropenia associated with myelodysplastic syndrome, hairy cell leukemia, aplastic anemia, acquired immune deficiency syndrome and zidovudine- and other drug-induced neutropenias. Pegfilgrastim has been used for peripheral blood stem cell leukapheresis prior to autologous stem cell transplantation. Sargramostim has also been used for non-FDA approved indications. It has been most commonly used to treat Crohn's disease. Other uses of sargramostim include the treatment of melanoma, neutropenia associated with myelodysplastic syndrome or aplastic anemia, oral mucositis, pulmonary alveolar proteinosis, sepsis and neutropenia in the newborn, stomatitis, zidovudine- and other drug-induced neutropenia and wound healing. Sargramostim has also been used as a vaccine adjuvant and an adjunct to high-dose chemotherapy.[15,16]

Pharmacokinetics

Table 3. Pharmacokinetics[1-5,17]

Generic Name(s)*	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Filgrastim	60 to 70 (SC)	Not reported	Not reported	3.5
Filgrastim-sndz	60 to 70 (SC)	Not reported	Not reported	3.5
Pegfilgrastim	Not reported	Not reported	Not reported	15 to 18
Sargramostim	Not reported	Not reported	Not reported	1 (IV) 2 to 3 (SC)
Tbo-Filgrastim	33*	Not reported	Not reported	3.2 to 3.8

SC=subcutaneous, IV=intravenous
*Absolute bioavailability based on a dose of 5 µg/kg injected subcutaneously.

Clinical Trials

The safety and efficacy of the granulocyte and granulocyte-macrophage colony stimulating factors have been evaluated in several clinical trials, however, there are few trials that compare G-CSFs to GM-CSFs.[18-53]

Two retrospective trials evaluated the differences in efficacy between filgrastim and pegfilgrastim in patients with nonmyeloid malignancies who underwent chemotherapy. In Almenar et al, a multicenter, retrospective, observational trial, pegfilgrastim was associated with fewer episodes of febrile neutropenia compared to filgrastim (10.7 vs 24.3%, respectively; P value not reported) as well as fewer hospitalizations for febrile neutropenia (9.3 vs 19.8%, respectively; P value not reported).[18] Results from Weycker et al also showed that the risk of hospitalization for febrile neutropenia or infection was lower with pegfilgrastim compared to filgrastim (odds ratio, 0.64; 95% CI, 0.48 to 0.85; P=0.002).[19]

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A multicenter, randomized, double-blind, active-control trial compared single-dose pegfilgrastim to daily filgrastim in reducing neutropenia in 310 patients who received four cycles of myelosuppressive chemotherapy for high-risk breast cancer. There were no significant differences between treatment groups in the duration of severe neutropenia and the depth of ANC nadir in all cycles. Overall, the incidence of febrile neutropenia was less in the pegfilgrastim group than in the filgrastim group (9 vs 18%; P=0.029). The difference in the mean duration of severe neutropenia between the pegfilgrastim and filgrastim treatment groups was less than one day. Adverse event profiles in the pegfilgrastim and filgrastim groups were similar. A single injection of pegfilgrastim per cycle was as safe and effective as daily injections of filgrastim in reducing neutropenia and its complications in patients who received four cycles of chemotherapy.[121]

One randomized, double-blind, multicenter trial compared filgrastim and sargramostim in 181 patients with chemotherapy-induced febrile neutropenia (absolute neutrophil count [ANC] ≤500 cells/µL). Patients were given daily subcutaneous injections of either agent until ANC levels reached ≥1,500 cells/µL. Overall, the mean number of days patients received filgrastim (4.60±0.14 days) was significantly shorter than sargramostim (5.70±0.23 days; *P*=0.0001). There was no significant difference among the treatment groups in the mean number of days to reach an ANC 500 cells/µL (filgrastim, 3.60±0.16 vs sargramostim, 3.30±0.16; *P*=0.32); however, the mean number of days to reach an ANC 1,000 and 1,500 cells/µL was significantly lower in the filgrastim group (4.50±0.13 and 4.60±0.14, respectively) compared to the sargramostim group (5.10±0.22 and 5.70±0.23, respectively; *P*=0.009 and *P*=0.0001, respectively). In regards to the other endpoints reported, patients in the sargramostim group had fewer hospitalizations with febrile neutropenia or intravenous (IV) antibiotics (*P*=0.46), shorter mean length of hospitalization (*P*=0.58) and shorter mean duration of fever (*P*=0.14) compared to patients in the filgrastim group; however, these endpoints did not reach statistical significance. Overall the agents were well tolerated and had comparable efficacy and tolerability in the treatment of standard-dose chemotherapy-induced myelosuppression in community practice.[22]

A second prospective, randomized, double-blind, multicenter trial comparing sargramostim and filgrastim published by the same author found that with the exception of a slightly higher incidence of grade 1 fever (37.1 to 38.0°C) with sargramostim compared to filgrastim (48 vs 26%, respectively; *P*=0.01), there were no statistically significant differences in the incidence or severity of local or systemic adverse events potentially related to CSFs. Although the study was not designed to evaluate efficacy directly, there were also no statistically significant differences between treatment groups in total days of growth factor therapy, days of hospitalization or days of IV antibiotic therapy during the treatment period. Both agents were well tolerated and there were no clinically significant differences between them.[23]

A Cochrane review of 13 randomized, placebo-controlled trials was performed to evaluate the efficacy and safety of G-CSF (filgrastim and lenograstim [not available in the United States]) or GM-CSF (sargramostim) compared to placebo in patients who were receiving nonmyeloablative chemotherapy for malignant lymphomas. Sensitivity analyses that were performed in this review concluded that there were no differences between G-CSF and GM-CSF in their effects on overall survival, freedom from treatment failure and risk reduction in incidence of neutropenia or febrile neutropenia.[24]

Two retrospective, case-controlled cohort trials were conducted to compare filgrastim, pegfilgrastim and sargramostim in reducing the risks of neutropenia-related hospitalizations in cancer patients receiving chemotherapies. Weycker et al found that the use of pegfilgrastim was associated with fewer hospitalizations for neutropenic complications compared to filgrastim and sargramostim (1.1, 2.1 and 2.5%, respectively; *P*<0.001 for both filgrastim and sargramostim compared to pegfilgrastim).[20] Heaney et al found that sargramostim was associated with fewer infection-related hospitalizations compared to filgrastim (12 vs 26%, respectively; *P*=0.0422) and pegfilgrastim (24%; *P*=0.0628). The incidence of hospitalizations for febrile neutropenia was also lower in the sargramostim group compared to the filgrastim and pegfilgrastim groups; however, these differences were not statistically significant.[25]

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Additional studies that compared filgrastim to sargramostim were done. In these studies, efficacy favored filgrastim overall. Filgrastim had statistically significant fewer episodes of fever in nonmyeloid malignancies in patients receiving myelosuppressive anticancer drugs (P<0.001).[37] For collection of progenitor cells by leukapheresis, the filgrastim group had significantly greater CD34+ harvested than the sargramostim group (P=0.0001). Additionally, ANC recover was significantly more rapid in the filgrastim group and there were significantly fewer patients with a temperature >38.5^{o}, patients who received IV antibiotics or red blood cells and hospital admissions.[44] One study had mixed results that showed sargramostim improved time to ANC recover compared with filgrastim, but required a greater number of days with growth factor (P<0.001 and P=0.001, respectively). In this study, there were no differences between time to platelet recovery, number of days patients experienced fever or received IV antibiotics, the number of platelet transfusions and the number of red blood cell units received.[50]

Tbo-filgrastim was evaluated in a single multi-center, placebo- and active-controlled, randomized control trial that evaluated patients with breast cancer. Patients received tbo-filgrastim, filgrastim, or placebo for cycle one. For cycle two to four, patients that received placebo were switched to tbo-filgrastim. Doses were 5µg/kg daily for both active treatment groups for all cycles. The primary efficacy endpoint was duration of severe neutropenia in cycle one. When compared to placebo, tbo-filgrastim was provided a statistically significant improvement in duration of severe neutropenia (no P value reported). When compared to filgrastim, tbo-filgrastim was considered equivalent with a least square mean difference of 0.028 (95% CI, -0.262 to 0.325). Secondary endpoints showed no differences between tbo-filgrastim and filgrastim during any cycle or overall.[38] Two additional studies published showed similar results but in patients with aggressive non-Hodgkin's lymphoma and small cell or non-small cell lung cancer.[39,40]

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Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Decrease Incidence of Infection, as Manifested by Febrile Neutropenia, in Patients with Nonmyeloid Malignancies Receiving Myelosuppressive Anticancer Drugs Associated with Significant Incidence of Severe Neutropenia with Fever				
Almenar et al[18] Filgrastim or lenograstim daily (dosing not specified) vs pegfilgrastim (dosing not specified)	MC, OS, RETRO Patients with nonmyeloid tumors who underwent cytotoxic chemotherapy; tumor types included breast, lung, NHL, multiple myeloma, gastrointestinal, gynecological and others	N=186 Duration not specified	Primary: Proportion of patients with proactive vs reactive use of G-CSF, the duration of treatment with daily G-CSF, delay or reduction in chemotherapy dose (>3 days delay with respect to planned date of administration or <85% of planned dose administered), incidence of febrile neutropenia, incidence of hospitalization, antibiotic use, adverse events Secondary: Not reported	Primary: The percentage of patients receiving G-CSF as primary and secondary prophylaxis for febrile neutropenia was similar in both filgrastim and pegfilgrastim groups. Pegfilgrastim was less likely to be used to treat febrile neutropenia compared to filgrastim (17.3 vs 29.7%; P value not reported). The duration of treatment with daily G-CSF was not reported. Similar percentage of patients had a delay in chemotherapy administration in the filgrastim and pegfilgrastim groups (46.0 and 44.0%, respectively; P value not reported). However, 20.7% of patients receiving filgrastim had a chemotherapy dose reduction due to neutropenia, compared to 6.7% of patients receiving pegfilgrastim (P value not reported). There were fewer incidences of febrile neutropenia and hospitalization due to febrile neutropenia in the pegfilgrastim group compared to the filgrastim group. The incidences of febrile neutropenia in the filgrastim and pegfilgrastim groups were 24.3 and 10.7%, respectively (P value not reported), while the incidences of hospitalization due to febrile neutropenia were 19.8 and 9.3%, respectively (P value not reported). Fewer patients in the pegfilgrastim group received treatment of antibiotics due to febrile neutropenia compared to the filgrastim group (8.0 vs 17.1%; P value not reported). Bone pain was reported in 2.7 and 1.3% of patients in the filgrastim and pegfilgrastim groups, respectively. Other treatment-related adverse events were reported in 5.4 and 1.3% of patients in the filgrastim and pegfilgrastim groups, respectively (P value not reported).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Weycker et al[19] Filgrastim (dose not specified) for a mean of 4.5±3.3 days vs pegfilgrastim (dose not specified) G-CSFs were administered on or before day 5 of each chemotherapy cycle.	CO, RETRO Adult patients who received chemotherapy for a primary solid tumor and who received filgrastim or pegfilgrastim during the first course of chemotherapy; the most common types of malignancies were breast cancer, lung cancer and NHL; eligible, unique chemotherapy cycles were then identified; cycles were eligible if the first and second cycles were 20 to 59 days apart and if G-CSFs were administered on or before day 5 of cycle; receipt of chemotherapy and diagnoses of	N=4,903 (patients with a total of 15,763 chemo-therapy cycles) Duration not specified	Primary: Incidence of hospitalization for neutropenia, incidence of hospitalization for febrile neutropenia or infection, incidence of all-cause hospitalization (hospitaliza-tions for neutropenia, febrile neutropenia and infection were identified using corresponding ICD-9 codes) Secondary: Not reported	Primary: Pegfilgrastim was associated with lower incidence of hospitalizations for neutropenia compared to filgrastim (1.2 vs 2.1%; OR, 0.55; 95% CI, 0.36 to 0.84; P=0.005). The risk of hospitalization for neutropenic fever or infection was also lower with pegfilgrastim than filgrastim (3.1 vs 4.8%; OR, 0.64; 95% CI, 0.48 to 0.85; P=0.002). The incidence of all-cause hospitalizations was 6.3% with pegfilgrastim and 8.7% with filgrastim (OR, 0.70; 95% CI, 0.56 to 0.86; P=0.001). After adjusting for patient, cancer and chemotherapy characteristics, pegfilgrastim was still associated with a lower incidence of hospitalization for neutropenia (adjusted OR, 0.64; 95% CI, 0.41 to 0.99; P=0.043), hospitalization for neutropenic fever or infection (adjusted OR, 0.69; 95% CI, 0.52 to 0.92; P=0.012) and all-cause hospitalization (adjusted OR, 0.73; 95% CI, 0.59 to 0.91; P=0.004). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	malignancies were based on medical insurance claims			
Weycker et al[20] Pegfilgrastim vs filgrastim (dose not specified) for 4.8±3.4 days or sargramostim (dose not specified) for 6.0±4.4 days G-CSFs and GM-CSF were administered on or before day 5 of each chemotherapy cycle. The most common concomitant chemotherapy regimen was cyclophosphamide and doxorubicin for breast cancer, carboplatin and etoposide for lung cancer and cyclophosphamide,	CO, RETRO Adult patients who received chemotherapy for solid tumors based on evidence of medical claims; each chemotherapy cycle was a minimum of 20 days; the most common malignancies were breast cancer, lung cancer and NHL; eligible, unique chemotherapy cycles were then identified; cycles were eligible if the first and second cycles were 20 to 59 days apart and if G-CSFs and GM-CSF were administered on or before day 5 of	N=22,995 (patients with a total of 77,269 chemo-therapy cycles) Duration not specified	Primary: Incidence of hospitalization for neutropenia, incidence of hospitalization for neutropenic fever or infection, incidence of all-cause hospitalization within 60 days after the initiation of study drugs (hospitalize-tions for neutropenia, febrile neutropenia and infection were identified using corresponding ICD-9 codes) Secondary: Not reported	Primary: The risk of hospitalization for neutropenia was higher during chemotherapy cycles in which patients received filgrastim compared to pegfilgrastim (2.1 vs 1.1%, respectively; OR, 1.93, 95% CI, 1.63 to 2.28; P<0.001). Similarly, the same risk was higher in patients who received sargramostim during chemotherapy compared to pegfilgrastim (2.5 vs 1.1%, respectively; OR, 2.39, 95% CI, 1.76 to 3.26; P<0.001). A similar trend was seen in the risk of hospitalization for neutropenic fever or infection. Pegfilgrastim was associated with fewer hospitalizations compared to filgrastim (2.6 vs 4.0%, respectively; OR, 1.53; 95% CI, 1.35 to 1.72; P<0.001) and sargramostim (5.1%; OR, 1.98; 95% CI, 1.59 to 2.46; P<0.001). Patients receiving pegfilgrastim had fewer incidence of all-cause hospitalization (5.3%) compared to filgrastim (7.9%; OR, 1.55; 95% CI, 1.42 to 1.69; P<0.001) and sargramostim (9.6%; OR, 1.91; 95% CI, 1.62 to 2.25; P<0.001). After adjusting for patient, cancer and chemotherapy characteristics, filgrastim and sargramostim were still associated with increased risk of hospitalization for neutropenia compared to pegfilgrastim (OR, 1.8 for filgrastim; P<0.001; OR, 2.7 for sargramostim; P<0.001). Secondary: Not reported

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
doxorubicin and vincristine for NHL.	cycle; receipt of chemotherapy and diagnoses of malignancies were based on medical insurance claims			
Holmes, O'Shaughnessy et al[21] Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC ≥10x10^9 cells/µL after the expected nadir or for 14 days, whichever occurred first vs pegfilgrastim 100 µg/kg SC on day 2 of each cycle Subjects received doxorubicin and docetaxel chemotherapy repeated every 3 weeks for up to 4 cycles provided ANC >1x10^9 cells/µL, and platelet count >100x10^9 units/L.	DB, MC, RCT Subjects >18 years of age diagnosed with high risk stage II or stage III/IV breast cancer, who were naïve to chemotherapy or received adjuvant therapy and/or completed ≤1 regimen of chemotherapy for metastatic disease, completion of previous chemotherapy more than four weeks before randomization, an ECOG performance status ≤2, an ANC ≥1.5x10^9/L, platelet count	N=310 4 cycles of chemo-therapy	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9 cells/µL) in cycle one Secondary: Duration of grade 4 neutropenia during cycles two through four, the depth of ANC nadir in each of the cycles (one to four), rates of febrile neutropenia and the time to ANC recovery in chemotherapy cycles one to four	Primary: There was no significant difference in duration of grade 4 neutropenia in cycle one between the filgrastim group (1.8 [1.4] days) and the pegfilgrastim group (1.7 [1.5] days; difference of 0.03 days; 95% CI, –0.36 to 0.30). Secondary: The duration of grade 4 neutropenia was significantly less in the pegfilgrastim group in cycles two to four compared to filgrastim: cycle two: 0.7 vs 1.1 days, respectively (difference of –0.40 days; 95% CI, –0.64 to –0.17; P=0.001); cycle three: 0.6 vs 1.2 days, respectively (difference of –0.63; 95% CI, –0.91 to –0.36; P≤0.001); cycle four: 0.9 vs 1.3 days (difference of –0.38 days; 95% CI, –0.71 to –0.07; P=0.019). The depth of ANC nadirs was similar between the two treatment groups over the course of the study (P values not reported). Febrile neutropenia occurred at least once during the study in 9% of patients in the pegfilgrastim group which was significantly less than the 18% of patients in the filgrastim group (difference of –9%; 95% CI, –16.8 to –1.1; P=0.029). The mean time to ANC recovery was 9.3 days for the pegfilgrastim group and 9.7 days for the filgrastim group (difference of –0.40 days; 95% CI, –0.88 to 0.08; P value not reported). Adverse event profiles in the pegfilgrastim and filgrastim groups were similar.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	≥100x10^9/L, and adequate hepatic and cardiac function			
Beveridge et al[22] Filgrastim 5 µg/kg SC daily vs sargramostim 250 µg/m^2 SC daily	DB, MC, RCT Patients ≥18 years of age who developed neutropenia within four weeks of chemotherapy regimen and had an ANC <500 cells/µL	N=181 Mean duration of treatment: filgrastim, 4.60±0.14 days; sargra-mostim, 5.70±0.23 days	Primary: Number of days to reach an ANC 1,000 and 1,500 cells/µL, number of febrile neutropenic episodes, duration of hospitalization, duration of fever, duration of IV antibiotic therapy, number of episodes of chills or fever, number of events of fever in the morning, evening and four hours after injection of CSF, documented positive bacterial cultures, number of events of sepsis and adverse events Secondary: Not reported	Primary: The number of days to reach an ANC 1,000 cells/µL was significantly fewer with filgrastim compared to sargramostim (4.50±0.13 vs 5.10±0.22 days; P=0.009). Similarly, filgrastim was associated with fewer number of days to reach an ANC 1,500 cells/µL compared to sargramostim (4.60±0.14 vs 5.70±0.23 days; P=0.0001). There was no significant difference between the two treatment groups with regard to the number of days to reach an ANC 500 cells/µL (3.60±0.16 vs 3.30±0.16 days; P=0.32). There was no significant difference between filgrastim and sargramostim regarding the proportion of patients with hospitalizations for febrile neutropenia or IV antibiotic therapy (6.3 and 7.8%, respectively; P=0.46). Compared to filgrastim, sargramostim was associated with a shorter duration of hospitalization (5.60±1.10 vs 4.80±0.58 days; P=0.58), fever (3.60±0.92 vs 1.60±0.60 days; P=0.14) and IV antibiotic therapy (6.30±1.3 vs 4.70±0.67 days; P value not reported). Two patients (1.9%) in the filgrastim group and one patient (1.2%) from the sargramostim group experienced chills (P=0.60). There was no significant difference between filgrastim and sargramostim with respect to the incidence of Grade 2 fever reported in the morning (10 and 9%, respectively; P=0.53), evening (13.7 and 11.0%, respectively; P=0.41) and four hours after CSF injection (10.7 and 3.8%, respectively; P=0.07). Two patients receiving filgrastim and no patient receiving sargramostim had documented positive blood cultures, indicating bacteremia (P value not reported). However, the incidence of sepsis was not reported.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both filgrastim and sargramostim were well-tolerated, and there was no statistically significant difference between the two treatment groups with regard to the incidence of adverse events. Secondary: Not reported
Beveridge et al[23] Filgrastim 7 µg/kg daily vs sargramostim 300 µg daily Study drugs were administered starting one to two days after chemotherapy, chemotherapy regimens were not specified in the protocol.	DB, MC, RCT Patients ≥18 years of age, documented malignancy and an ECOG performance status grade 0 to 2 and received cytotoxic chemotherapy	N=144 7 days	Primary: Tolerability, hospitalization and use of IV antibiotics Secondary: Not reported	Primary: Both agents were well tolerated. There were no cases of grade 4 toxicity during the treatment period in patients receiving either sargramostim or filgrastim and no instances when either drug had to be discontinued because of toxicity (P values not reported). Grade 1 fever (37.1 to 38.0°C) occurred in significantly more patients in the filgrastim group (36 patients) compared to the sargramostim group (16 patients; P<0.01). There were no statistically significant differences between treatment groups in the incidence of local reactions or in the incidence or severity of bone or joint pain, chills, nausea, vomiting, dyspnea or headache (P values not reported). There were no significant differences between the filgrastim and sargramostim groups in days of hospitalization (4.0 vs 4.6 days, respectively) and in days of IV antibiotic therapy (6.0 vs 4.4 days, respectively) during the treatment period (P values not reported). Secondary: Not reported
Bohlius et al[24] Filgrastim or lenograstim* ≥1 µg/kg/day IV or SC or	MA of 13 PC, RCT Patients >16 years of age with NHL or HD	N=2,607 Duration not specified	Primary: Overall survival, freedom from treatment failure Secondary: Quality of life, risk	Primary: When compared to placebo, treatment with CSFs had no significant effect on the overall survival (HR, 0.97; 95% CI, 0.87 to1.09; P value not reported) or freedom from treatment failure (HR, 1.11; 95% CI, 0.91 to1.35; P value not reported). Sensitivity analyses were performed and showed that there was no

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sargramostim ≥1 µg/kg/day IV or SC vs placebo or no treatment All patients received G-CSF or GM-CSF as primary prophylaxis during standard nonmyeloablative chemotherapy prior to the onset of neutropenia in the first- or second-line treatment of malignant lymphoma. G-CSF and GM-CSF was given within 72 hours of chemotherapy administration and in each cycle of chemotherapy.			and duration of neutropenia, risk and duration of febrile neutropenia, infection, risk and duration of IV antibiotic treatment, hospitalization, dose intensity of chemotherapy, mortality during chemotherapy, tumor response, adverse effects of CSFs, risk and duration of thrombo-cytopenia and anemia	significant difference between G-CSF and GM-CSF in their effects on the primary endpoints. Secondary: No difference in quality of life was detected between CSF and placebo. Treatment with CSFs was associated with a 33% risk reduction in developing neutropenia (RR, 0.67; 95% CI, 0.60 to 0.73; P value not reported). There was a 26% risk reduction in developing febrile neutropenia with an ANC <$1x10^9$/L (RR, 0.74; 95% CI, 0.62 to 0.89; P value not reported) and a 41% risk reduction in developing neutropenia with ANC <$0.5x10^9$/L (RR, 0.59; 95% CI, 0.48 to 0.72; P value not reported) with CSF compared to placebo. There was no significant difference with respect to G-CSF compared to GM-CSF. There was no conclusive evidence that CSFs reduce the duration of neutropenia or febrile neutropenia. The risk of developing an infection was also reduced by 26% in patients receiving CSF compared to patients receiving placebo (RR, 0.74; 95% CI, 0.64 to 0.85; P value not reported). There was a non-significant risk reduction in requiring IV antibiotic treatment with CSF compared to placebo (RR, 0.82; 95% CI, 0.57 to 1.18; P value not reported). There was no conclusive evidence to detect the effect of CSF on the duration of IV antibiotic treatment, hospitalization or dose intensity of chemotherapy. Between the two treatment groups, there was no difference in mortality during chemotherapy (RR, 0.93; 95% CI, 0.60 to 1.43; P value not reported) or complete tumor response (RR, 1.03; 95% CI, 0.95 to 1.10; P value not reported). Significantly more patients receiving CSF reported bone pain compared to patients receiving placebo (RR, 3.57; 95% CI, 2.09 to 6.12; P value not reported). GM-CSF was associated with a smaller risk of bone pain

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to G-CSF (P=0.026). Treatment with CSF did not increase the risk of thromboembolic complications compared to placebo (RR, 1.29; 95% CI, 0.56 to 3.01; P value not reported). There was no conclusive evidence showing that CSF treatment affects incidence or degree of thrombocytopenia or anemia.
Heaney et al[25] Sargramostim (dose not specified) vs filgrastim (dose not specified) or pegfilgrastim (dose not specified)	CO, RETRO Adult patients with cancer who had received chemotherapy and had at least two doses of filgrastim or sargramostim or at least one dose of pegfilgrastim; the most common types of malignancies were breast cancer, lung cancer and NHL; patients receiving sargramostim were matched 1:1 with patients receiving filgrastim and pegfilgrastim based and gender and age	N=2,962 Average duration of treatment: filgrastim and sargra-mostin, 31 days; peg-filgrastim, 58 days	Primary: Incidence of infection-related hospitalization, associated costs per patient per month Secondary: Incidence of febrile neutropenia-related hospitalization	Primary: Sargramostim was associated with fewer infection-related hospitalizations compared to filgrastim (12 vs 26%, respectively; incidence rate ratio, 0.46; 95% CI, 0.22 to 0.97; P=0.0422) and pegfilgrastim (12 vs 24%; incidence rate ratio, 0.52; 95% CI, 0.26 to 1.04; P=0.0628). Comparison on febrile neutropenia-related hospitalizations was not performed due to low event rate in each treatment group. The per-patient-per-month costs for sargramostim was 84% lower compared to filgrastim ($138/patient/month vs $866/patient/month; P=0.0380) and 62% lower compared to pegfilgrastim ($138/patient/month vs $365/patient/month; P=0.01). Secondary: Patients receiving sargramostim had fewer febrile-neutropenia-related hospitalizations compared to filgrastim and pegfilgrastim, though the differences were not statistically significant. The incidence of hospitalizations was 5% for sargramostim, 8% for filgrastim (incidence rate ratio to sargramostim, 0.58; 95% CI, 0.17 to 1.98; P=0.3837) and 6% for pegfilgrastim (incidence rate ratio, 0.85; 95% CI, 0.26 to 2.75; P=0.0628).
Grigg et al[32]	MC, OL, RCT	N=50	Primary: Duration of grade	Primary: The mean duration of grade 4 neutropenia in cycle one was shorter with

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Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC ≥10x10^9 cells/µL after the expected nadir or for 14 days, whichever occurred first vs no cytokine support in cycle 1 followed by filgrastim 5 µg/kg/day SC in all other cycles vs pegfilgrastim 60 µg/kg on day 2 of each cycle vs pegfilgrastim 100 µg/kg on day 2 of each cycle Subjects received CHOP therapy repeated every three weeks for up to six cycles provided ANC >1x10^9 cells/µL, and platelet count >100x10^9 units/L.	Subjects ≥60 years of age diagnosed with NHL requiring treatment with standard CHOP therapy, ECOG performance status ≤2, an ANC ≥2x10^9 cells/µL, platelet count ≥100x10^9/L, bilirubin concentration ≤2xupper limit of normal, and adequate renal function	6 cycles of chemo-therapy	4 neutropenia (ANC <0.5x10^9/L) in cycle one Secondary: Incidence of febrile neutropenia (ANC <0.5x10^9 cells/µL and temperature >38.2°C), the time to ANC recovery (ANC ≥2.0x10^9 cells/µL) in cycles one, three and six and the ability to deliver planned dose of chemotherapy on time	the patients who received cytokine (pegfilgrastim 60 µg/kg, 2.2±1.2 days; pegfilgrastim 100 µg/kg, 1.5±1.0 days; filgrastim 0.8±1.2 days) compared to the patients who received no cytokine in cycle one (mean 5.0±2.0 days; P values not reported). Secondary: The incidence of febrile neutropenia throughout the study was as follows: four of 13 (31%) patients treated with pegfilgrastim 60 µg/kg who received a total of 68 cycles, zero of 13 patients treated with pegfilgrastim 100 µg/kg who received a total of 62 cycles, one of 13 (8%) patients treated with filgrastim who received a total of 59 cycles and zero of nine patients who did not receive cytokine (in cycle one only) who received a total of 43 cycles (P values not reported). The median time to ANC recovery in cycles one, three and six was similar for the all the groups receiving cytokine support: pegfilgrastim 60 µg/kg, 11 days (10 to 14); pegfilgrastim 100 µg/kg, 10 days (nine to 12) and filgrastim, 10 days (one to 20) (P values not reported). In cycles two to six, eight patients experienced a delay in the start of chemotherapy of more than three days; no delays were related to neutropenia. Full dose cyclophosphamide and doxorubicin was given in 94%, 96% and 100% of cycles given to filgrastim, pegfilgrastim 60 µg/kg and pegfilgrastim 100 µg/kg patients, respectively. One filgrastim patient received reduced doses due to error and one pegfilgrastim 60 µg/kg patient received reduced doses following febrile episodes. In addition, seven patients had a reduction in vincristine dose due to neuropathy (P values not reported). Pegfilgrastim was well tolerated with a safety profile similar to daily filgrastim. Adverse events (WHO grade 1 to 4) were reported by 95% of filgrastim and 96% of pegfilgrastim patients (P value not reported).
Holmes, Jones et al[33]	MC, RCT	N=154	Primary: Duration of grade	Primary: In cycle one, the mean duration of grade 4 neutropenia for filgrastim was

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Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC ≥$10x10^9$/L after the expected nadir or for 14 days, whichever occurred first vs pegfilgrastim 30 µg/kg SC on day 2 of each cycle vs pegfilgrastim 60 µg/kg SC on day 2 of each cycle vs pegfilgrastim 100 µg/kg SC on day 2 of each cycle Subjects received doxorubicin and docetaxel chemotherapy repeated every 3 weeks for up to 4 cycles provided ANC >$1x10^9$ cells/µL, and platelet count >100 x 10^9 units/L.	Woman ≥18 years of age diagnosed with high-risk stage II, III or IV breast cancer, ECOG performance status ≤2, WBC count ≥$4x10^9$ cells/µL, platelet count ≥$150x10^9$ units/L, adequate renal, hepatic and cardiac function	4 cycles of chemo-therapy	4 neutropenia (ANC <$0.5x10^9$ cells/L) in cycle one Secondary: Duration of grade 4 neutropenia during cycles two through four, ANC profile, time to ANC recovery (ANC ≥$2x10^9$ cells/µL) after the expected ANC nadir, and rate of febrile neutropenia (ANC <$0.5x10^9$ cells/µL and temperature >38.2°C)	1.6 days compared to 2.7 days for pegfilgrastim 30 µg/kg, two days for pegfilgrastim 60 µg/kg, and 1.3 days for pegfilgrastim 100 µg/kg (P values not reported). Secondary: The duration of grade 4 neutropenia in cycles two through four ranged between zero and one day in ≥98% for pegfilgrastim 100 µg/kg, compared to 86% for pegfilgrastim 60 µg/kg and ≥92% for filgrastim (P values not reported). Most patients in the pegfilgrastim 30 µg/kg group were escalated to higher doses of pegfilgrastim in later cycles and these values were not reported. Pegfilgrastim 100 µg/kg had similar ANC profiles as filgrastim in each of the cycles (P value not reported). The mean time to ANC recovery for cycle one was 11 days for pegfilgrastim 30 µg/kg and 10.3 days for 60 µg/kg, respectively, compared to 9.5 days for pegfilgrastim 100 µg/kg and 9.4 days for filgrastim 5 µg/kg/day. The mean time to ANC recovery was significantly longer for pegfilgrastim 30 and 60 µg/kg/cycle but not the 100 µg/kg/cycle, compared to filgrastim (P values not reported). Febrile neutropenia was experienced at least once during the study by seven patients (12%) with pegfilgrastim 60 µg/kg, five patients (11%) with pegfilgrastim 100 µg/kg and two patients (12%) with filgrastim. There were no significant differences demonstrated between the groups (P values not reported). The safety profiles of pegfilgrastim and filgrastim were similar.

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Green et al[34] Filgrastim 5 µg/kg/day SC from day 2 of each cycle until an ANC ≥$10x10^9$ cells/µL after the expected nadir or for 14 days, whichever occurred first vs pegfilgrastim 6 mg SC once on day 2 of each cycle Subjects received doxorubicin and docetaxel chemotherapy repeated every 3 weeks for up to 4 cycles provided ANC >$1x10^9$ cells/µL, and platelet count >$100x10^9$ units/L.	DB, MC, RCT Subjects >18 years of age diagnosed with high-risk stage II or stage III/IV breast cancer, ECOG performance status ≤2, chemotherapy naïve or adjuvant therapy only or only one chemotherapy regimen for metastatic disease, an ANC ≥$1.5x10^9$ cells/µL, platelet count ≥$100x10^9$ units/L, and a serum creatinine <1.5 times upper limit of normal	N=157 4 cycles of chemo-therapy	Primary: Duration of grade 4 neutropenia (ANC <$0.5x10^9$ cells/µL) in cycle one Secondary: Duration of grade 4 neutropenia in each of cycles two through four, depth of the ANC nadir in each of cycles two through four, incidence of febrile neutropenia, time to neutrophil recovery (ANC ≥$2x10^9$ cells/µL), incidence of IV antibiotic administration and hospitalization	Primary: There was no significant difference in the mean duration of grade 4 neutropenia in cycle one between the filgrastim group (1.6±1.1 days) and the pegfilgrastim group (1.8±1.4 days; difference of 0.23 days; 95% CI, –0.15 to 0.63). Secondary: There were no significant differences demonstrated between treatment groups in the mean duration of grade 4 neutropenia in cycles two through four. Mean duration of grade 4 neutropenia in the filgrastim vs pegfilgrastim group was as follows: cycle two: 0.9±1.0 vs 1.1±1.2 days, respectively; difference of 0.13; 95% CI, –0.20 to 0.47; cycle three: 0.9±1.1 vs 1.1±1.2 days, respectively; difference of 0.16; 95% CI, –0.20 to 0.51; cycle four: 1.0±1.3 vs 1.0±1.1 days, respectively; difference of 0.00 days; 95% CI, –0.39 to 0.39. The median ANC nadir was significantly different between the two treatment groups (P value not reported). The incidence of febrile neutropenia was not statistically significant between the filgrastim (10 [13%] patients) group and the pegfilgrastim group (15 patients [20%]; difference of –7%; 95% CI, –19 to 5). The median time to neutrophil recovery in all cycles was nine days from the day of chemotherapy administration for both the pegfilgrastim group and the filgrastim group (P values not reported). Rates of IV antibiotic administration (21 and 17%) and hospitalizations (31 and 18%) for the filgrastim and pegfilgrastim groups, respectively, were generally consistent with the results obtained for the incidence of febrile neutropenia (P values not reported). The safety profile of pegfilgrastim, assessed by adverse events, antibody formation and changes in laboratory values, was similar to that of filgrastim.

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Vose et al[35] Filgrastim 5 µg/kg/day SC starting on day 6, 1 day after completion of chemotherapy and given until ANC ≥10x10^9 cells/µL postnadir or for 12 days, whichever came first vs pegfilgrastim 100 µg/kg SC once on day 6, one day after completion of chemotherapy, of each cycle Chemotherapy consisted of etoposide, methylprednisolone, cisplatin and cytarabine and repeated every three weeks.	MC, OL, RCT Subjects ≥18 years of age with an ECOG performance status ≤2, an ANC ≥1.5x10^9 cells/µL, platelet count ≥100x10^9 cells/µL, and adequate renal function who were diagnosed with relapsed or persistent HD and had treatment failure from ≥1 prior chemotherapy regimen or a diagnosis of NHL and relapsed from or were refractory to first-line CHOP chemotherapy	N=66 4 cycles of chemo-therapy	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9 cells/µL) in cycle one Secondary: Duration of grade 4 neutropenia in subsequent cycles, ANC profiles, time to ANC recovery, and rates of febrile neutropenia (ANC <0.5x10^9 cells/µL and temperature ≥ 38.2°C) for cycles one and two	Primary: There was no significant difference in the duration of grade 4 neutropenia in cycle one between the filgrastim group (68%) and the pegfilgrastim group (69%). Secondary: The mean duration of grade 4 neutropenia was not significantly different between the filgrastim group (0.6 days) and pegfilgrastim group (0.4 days; difference of –0.14; 95% CI, –0.73 to 0.44). The geometric mean ANC nadir was 0.208x10^9 cells/µL for the filgrastim group and 0.161x10^9 cells/µL for the pegfilgrastim group (95% CI, 0.326 to 1.839; P value not reported). The median time to ANC recovery was not significantly different between the filgrastim group (15 days) and pegfilgrastim group (16 days; 95% CI, –0.84 to 3.07). The rates of febrile neutropenia was not significantly different between the filgrastim group (19%) and pegfilgrastim group (21%; difference of 1.3%; 95% CI, –19.4 to 22.0). Reported side effects were similar between the two treatment groups.
Staber et al[36] Filgrastim 5 µg/kg/day SC from day 7 after transplantation until ANC >10x10^9 cells/µL vs	T Subjects with hematological malignancies, an ECOG performance status ≤2 and normal cardiac,	N=54 Duration not specified	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9 cells/µL) Secondary: Incidence of febrile	Primary: The mean duration of grade 4 neutropenia was significantly shorter in the pegfilgrastim group (8.3 days [8 to 14]) compared to the filgrastim group (9.5 days [5 to 14]; P=0.047). Secondary: There was no significant difference in the incidence of febrile neutropenia between the filgrastim group (23 patients [77%]) compared to the pegfilgrastim group (24 patients [80%]; P value not reported).

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pegfilgrastim 6 mg SC once on day 5 after transplantation PBSCT was performed on day 0 with unmanipulated peripheral blood stem cells that were harvested using cyclophosphamide and G-CSF before the start of the study.	pulmonary, hepatic and renal function prior to transplantation		neutropenia (ANC <0.5x10^9 cells/µL and temperature ≥38.2°C), duration of febrile neutropenia, duration of fever and incidence of documented infections	The mean duration of febrile neutropenia was significantly shorter in the pegfilgrastim group (1.6 days [zero to five]) compared to the filgrastim group (3.0 days [zero to nine]; P=0.017). The mean duration of fever was significantly shorter in the pegfilgrastim group (1.73 days [zero to five]) compared to the filgrastim group (4.1 days [zero to 16]; P=0.003). The incidence of documented infections was significantly less in the pegfilgrastim group (eight patients [26%]) compared to the filgrastim group (17 patients [56%]; P=0.02). Bone pain was the only adverse event considered cytokine related and was reported in six patients (20%) in the pegfilgrastim group and seven patients (23%) in the filgrastim group (P value not reported).
Milkovich et al[37] Filgrastim vs sargramostim Dosages of the medications were at the discretion of the investigator. Mean doses were 369 µg (5.5 µg/kg) for filgrastim and 474 µg (6.9 µg/kg) for sargramostim.	MC, RETRO, XO Subjects ≥18 years of age who received chemotherapy for a lung, breast, lymphatic system or ovarian tumor	N=490 12 months	Primary: Frequency and severity of adverse events and the frequency of switching to the alternative CSF Secondary: Not reported	Primary: Significantly more episodes of fever ≥100.4°F occurred in the sargramostim group (57 cycles [9%]) compared to the filgrastim group (39 cycles [4%]; P<0.001). Although skeletal muscle pain was the most frequently reported adverse event, there was no significant difference between the filgrastim group and the sargramostim group (11 vs 8%; P=0.06). Several adverse events occurred significantly more frequently in the sargramostim group compared to the filgrastim group: fatigue (4 vs 2%; P<0.05), diarrhea (3 vs 2%; P<0.05), injection site reaction (6 vs <1%; P<0.01), other dermatologic disorders (3 vs <1%; P<0.01) and edema (2 vs <1%; P<0.01). Significantly more patients switched from sargramostim to filgrastim (74 patients [29%]) compared to the number of patients who switched from filgrastim to sargramostim (two patients [1%]; P<0.001). The most common reason for switching from sargramostim to filgrastim was due to

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				an adverse event (45 patients [18%]) compared to zero patients who switched from filgrastim to sargramostim (P<0.001). Secondary: Not reported
del Giglio et al[38] Tbo-filgrastim(XM02) 5 µg/kg/day daily for five to 14 days vs filgrastim 5 µg/kg/day daily for five to 14 days vs placebo Patients who received placebo were switched to tbo-filgrastim therapy after cycle one. All patients underwent a maximum of four cycles of chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2)	AC, MC, PC, RCT Patients ≥18 years of age with breast cancer high risk stage II, III, or IV, planned treatment with docetaxel and doxorubicin, chemotherapy-naïve, Eastern Cooperative Oncology Group performance status ≤ 2, an ANC ≥1.5 x 10^9/L, platelet count ≥100 × 10^9/L, and adequate cardiac, hepatic and renal function	N=348 One cycle (primary endpoint) Four cycles (other endpoints)	Primary: Duration of severe neutropenia in cycle one Secondary: Duration of severe neutropenia in cycles two to four, incidence of observed and protocol febrile neutropenia by all cycles and across all cycles, depth of ANC nadir in cycles one to four, and time to ANC recovery in cycles one to four	Primary: Duration of severe neutropenia in the per-protocol groups were 1.1 days for both the tbo-filgrastim and filgrastim groups and 3.9 days for the placebo group. When compared to placebo, tbo-filgrastim provided a statistically significant improvement in duration of severe neutropenia (no P value reported). When compared to filgrastim, tbo-filgrastim was considered equivalent with a least square mean difference of 0.028 (95% CI, -0.262 to 0.325). Secondary: The mean duration of severe neutropenia in cycles two to four were similar in all treatment groups. Mean duration was 0.7, 0.7, and 0.5 days in cycle two, 0.6, 0.7, and 0.6 days in cycle three, and 0.7, 0.7, and 0.6 days in cycle four in the tbo-filgrastim, filgrastim, and placebo/tbo-filgrastim group (treated with tbo-filgrastim in cycles two to four), respectively. In cycle one, the incidence of observed or protocol defined febrile neutropenia was numerically lower in the tbo-filgrastim and filgrastim groups (12.1% and 12.5%, respectively) compared to the placebo group (36.1%); however, there were no significant differences with regard to febrile neutropenia incidence between the tbo-filgrastim and filgrastim groups neither in cycle one nor across all cycles. In cycle one in the placebo group, mean ANC values decreased after day two and reached a nadir on day 11, whereas in the tbo-filgrastim and filgrastim groups, mean values increased, reaching a maximum on day three, and then decreased to a nadir on day seven. Thereafter, mean values in the active treatment groups distinctly increased again, reaching a maximum on day 11. On day 21, mean values returned to values as

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				observed on day one in all treatment groups. In the subsequent cycles, all treatment groups demonstrated the same trends as for tbo-filgrastim and filgrastim in cycle one. In cycle one, the mean ANC nadir was deeper in the placebo group (0.2 x 10^9/L) compared to tbo-filgrastim and filgrastim groups (0.7 x 109/L). In cycles two, three, and four, the mean ANC nadir was not as deep as in cycle one and was similar across treatment groups with a mean value of approximately 1.0 x 109/L. In cycle one, the median time to ANC recovery was shorter in the tbo-filgrastim and filgrastim groups (8.0 and 8.0 days) compared to the placebo group (15.0 days). In cycles two, three, and four, the time to ANC recovery was similar in all treatment groups with a median of 8.0 days.
Engert et al[39] Tbo-filgrastim(XM02) 5 µg/kg/day daily for five to 14 days vs filgrastim 5 µg/kg/day daily for five to 14 days Patients that received filgrastim were switched to tbo-filgrastim therapy in subsequent cycles.	AC, MC, PC, RCT Patients ≥18 years of age with aggressive non-Hodgkin's lymphoma, planned/eligible to receive the CHOP regimen as routine chemotherapy, were chemotherapy-naïve, had a life-expectancy of at least six months, had an IPI score 3, ANC 1.5 x 109/L, platelet count 100x109/L,	N=92 Six cycles	Primary: Duration of severe neutropenia in cycles one and four, incidence of observed and protocol defined febrile neutropenia by cycle and across all cycles, depth of ANC nadir in cycles one and four and time to ANC recovery in cycles one and four Secondary: Not reported	Primary: Mean duration of severe neutropenia was 0.5 and 0.9 days in cycle one for tbo-filgrastim and filgrastim, respectively, and 0.2 and 0.7 days in cycle four after the switch from filgrastim to tbo-filgrastim in the reference group. The estimated treatment difference was -0.378 days (95% CI, -0.837 to 0.081, P=0.1055). In cycle one, incidences of observed or protocol defined febrile neutropenia were 11.1% for tbo-filgrastim group and 20.7% for filgrastim group (P=0.1232). Across all cycles, the incidence of observed or protocol defined febrile neutropenia was 31.7% and 41.4% in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively (P=0.2094). In cycle one in both treatment groups, mean ANC values increased after day two, reaching a maximum on day four and then decreased to a nadir on day nine. Thereafter, mean values increased again, reaching a maximum on day 11. On day 21, mean values approached those observed on day 1 in both treatment groups. The ANC profile was similar in cycles two to six. In cycle one, mean ANC nadir values were 1.7 x 109/L in the tbo-

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	and adequate hepatic, cardiac, and renal function			filgrastim group and 1.1 x 109/L in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim, mean ANC nadir values were 2.1 x 109/L and 1.8 x 109/L in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. In cycle one, mean time to ANC recovery was 6.0 days in the tbo-filgrastim group and 6.7 days in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, mean time to ANC recovery was 4.9 days and 6.1 days in the tbo-filgrastim and filgrastim tbo-filgrastim groups, respectively. Secondary: Not reported
Gatzemeir et al[40] Tbo-filgrastim(XM02) 5 µg/kg/day daily for five to 14 days vs filgrastim 5 µg/kg/day daily for five to 14 days Patients that received filgrastim were switched to tbo-filgrastim therapy in subsequent cycles.	AC, MC, PC, RCT Patients ≥18 years of age with small cell or non-small cell lung cancer planned/eligible to receive a platinum-based myelosuppressive chemotherapy, were chemotherapy-naive or had received no more than one previous chemotherapy regimen, had Eastern Cooperative	N=240 Six cycles	Primary: Duration of severe neutropenia in cycles one and four, the incidence of observed or protocol defined febrile neutropenia by cycle and across all cycles, the depth of ANC nadir in cycles one and four, and the time to ANC recovery in cycles one and four Secondary: Not reported	Primary: Mean duration of severe neutropenia was 0.5 and 0.3 days in cycle one for tbo-filgrastim and filgrastim groups, respectively, and 0.4 and 0.3 days in cycle four after the switch from filgrastim to tbo-filgrastim in the reference group. In the analysis of covariance for duration of severe neutropenia in cycle one, the estimated treatment difference was 0.157 days (95% CI, -0.114 to 0.428, no P value reported). In cycle one, incidences of observed or protocol defined febrile neutropenia were 15.0% for the tbo-filgrastim group and 8.8% for filgrastim group (P=0.2347), and in cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, incidences were 4.3% and 3.3%, respectively (P=0.9036). Across all cycles, the incidence of observed or protocol defined febrile neutropenia was 33.1% and 23.8% in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. In cycle one in both treatment groups, mean ANC values increased after day two, reaching a maximum on day five and then decreased to a nadir on day 11 (day 12 for filgrastim group). Thereafter, mean values increased again, reaching a maximum on day 14. On day 21, mean values approached those observed on day one in both treatment groups.

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	Oncology Group performance status 2, an ANC 1.5 x 109/L, platelet count 100 x 109/L, and adequate hepatic, cardiac, and renal function			The ANC profile was similar in cycles 2 to 6. In cycle one, mean ANC nadir values were 2.1 x 109/L in the tbo-filgrastim group and 2.9 x 109/L in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, mean ANC nadir values were 2.3 x 109/L and 3.2 x 109/L in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. In cycle one, mean time to ANC recovery was 6.3 days in the tbo-filgrastim group and 4.5 days in the filgrastim group. In cycle four, after switch from filgrastim to tbo-filgrastim in the reference group, mean time to ANC recovery was 6.4 days and 4.5 days in the tbo-filgrastim and filgrastim/tbo-filgrastim groups, respectively. Secondary: Not reported
Acceleration of Myeloid Recovery in Patients with Non-Hodgkin's Lymphoma, Acute Lymphocytic Leukemia and Hodgkin's Disease Undergoing Autologous Bone Marrow Transplant				
Nemunaitis et al[26] Sargramostim 250 µg/m^2/day IV beginning within four hours of bone marrow reinfusion and continuing for 21 days vs placebo Preparative regimens used before transplantation differed among the participating	DB, MC, PC, RCT Patients with relapsed NHL, HD and ALL who were undergoing an autologous BMT	N=128 100 days	Primary: Neutrophil recovery (ANC ≥500x10^6 cells/L) Secondary: Infections, duration of IV antibiotics, duration of hospitalization	Primary: The patients in the sargramostim group had a significantly shorter time to ANC recovery compared to the patients in the placebo group (19 vs 26 days, respectively; P<0.001). Secondary: The patients in the sargramostim group had significantly fewer non-streptococcal infections compared to the patients in the placebo group (P<0.004). The patients in the sargramostim group had a significantly shorter duration of IV antibiotic use compared to the patients in the placebo group (24 vs 27 days, respectively; P=0.009). The patients in the sargramostim group had a significantly shorter duration of hospitalization compared to the patients in the placebo group (27 vs 33 days, respectively; P=0.01).

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institutions.				There were no significant differences in incidence and duration of fever, frequency of other side effects or 100-day survival rate between the two groups.
Lazarus et al[27] RhGM-CSF 11 µg/kg/day IV beginning three hours after completion of marrow infusion then daily thereafter over four hours until either recovery of both neutrophil count (>1,500 cells/µL) and platelet count (>50,000 units/µL, untransfused) occurred, or CSF therapy was administered for a total of 30 days vs historical control group Treatment consisted of involved-field radiotherapy, cyclophosphamide 60 mg/kg/day IV for two days, fractionated total body irradiation and autologous BMT.	MC Patients 15 to 60 years of age with histologically confirmed NHL in relapse	N=16 Duration not specified	Primary: Neutrophil recovery (ANC $\geq$500 cells/mm^3), time to self-sustaining platelet count >20,000 units/µL, toxicity, hematopoietic reconstitution Secondary: Not reported	Primary: Neutrophil recovery was significantly faster in the rhGM-CSF group (14 days [9 to 30 days]) compared to the control group (20 days [12 to 51 days]; P=0.00002). Time to self-sustaining platelet count >20,000 units/µL was not significantly different between the rhGM-CSF group (23.5 days [12 to 100 days]) and the control group (26 days [7 to 149]; P=0.38). Toxicities encountered were mild and included fever, chills, hypertension, alopecia, rash, diarrhea, stomatitis, myalgias and synovial (knee) effusions. All patients showed early regeneration of hematopoietic precursors in the bone marrow between days 10 and 22 after transplantation and increased in proportion to peripheral blood counts, but by 30 to 60 days still remained much lower than before transplant. Neutrophils transiently decreased in 13 of 16 patients (median decrease, 42%) within 24 to 72 hours of discontinuing rhGM-CSF infusions. Secondary: Not reported

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Rabinowe et al[28] Sargramostim 250 µg/m^2/day IV beginning within four hours of bone marrow reinfusion and continuing for 21 days vs placebo Patients originally participated in an efficacy study conducted by Nemunaitis et al.[23]	ES Patients with relapsed NHL, HD and ALL who underwent an autologous BMT	N=128 36 months	Primary: Long-term toxicities, clinical variables likely to predict for the speed of neutrophil engraftment and the independent predictive effect of sargramostim on neutrophil recovery Secondary: Not reported	Primary: There were no significant differences between the sargramostim group and the placebo group in disease-free survival (P=0.58) or in overall survival (P=0.55). Those patients with the diagnosis of HD demonstrated delayed neutrophil recovery to both an ANC ≥100 and ≥500 cells/µL (P=0.07) in comparison to patients with NHL or leukemia. Patients with HD and previous exposure to stem cell depleting agents experienced a significant delay in neutrophil recovery to an ANC of ≥500/µL (P=0.0008). Sargramostim accelerated neutrophil recovery following marrow infusion regardless of disease type (P=0.0011), previous exposure to agents that deplete stem cells (P=0.0028), prior number of drugs (P=0.0035), radiotherapy exposure (P=0.0024), marrow purging (P=0.0028), type of preparative regimen (P=0.0023) or relapse status at autologous BMT (P=0.0031). Secondary: Not reported
Acceleration of Myeloid Recovery in Patients Undergoing Allogeneic Bone Marrow Transplant from Human Leukocyte Antigen-Matched Related Donors				
Nemunaitis et al[29] Sargramostim 250 µg/m^2/day by 4-hour infusion starting on the day of marrow infusion and continuing to day 20 vs	DB, MC, PC, RCT Patients of all ages and of either sex undergoing HLA-identical sibling BMT for hematologic malignancy	N=109 1 year	Primary: Time to myeloid engraftment (ANC ≥500 cells/mm^3), time to ANC ≥1,000/mm^3, median days of hospitalization Secondary: Rate of infections,	Primary: The median time to myeloid engraftment was significantly less in the sargramostim group (13 days) compared to the placebo group (17 days; P=0.0001). The median time to ANC ≥1,000/mm^3 was significantly less in the sargramostim group (14 days) compared to the placebo group (19 days; P=0.0001). The median days of hospitalization was significantly less in the sargramostim group (25 days) compared to the placebo group (26 days;

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placebo All patients received HLA-identical sibling marrow and cyclosporine and prednisone for GVHD prophylaxis.			rate of bacteremia, rate of grade 3 or 4 mucositis	P=0.02). Secondary: The rate of infections was significantly less in the sargramostim group (34 patients) compared to the placebo group (51 patients; P=0.001). The rate of bacteremia was significantly less in the sargramostim group (9 patients) compared to the placebo group (19 patients; P=0.043). The rate of grade 3/4 mucositis was significantly less in the sargramostim group (four patients) compared to the placebo group (16 patients; P=0.005). There were no significant differences between the two groups in platelet recovery, erythrocyte recovery, and incidence of veno-occlusive disease, GVHD severity, relapse or survival.
Chronic Administration to Reduce Incidence and Duration of Sequelae of Neutropenia in Symptomatic Patients with Congenital, Cyclic or Idiopathic Neutropenia				
Bernini et al[30] RhG-CSF 5 µg/kg SC once daily until ANC >1.5x10^9 cells/L The rhG-CSF dosage, interval and amount were then increased and decreased, respectively, in an alternating fashion until the lowest rhG-CSF dose that would maintain the ANC >1x10^9 cells/L was reached.	T Children with symptomatic chronic idiopathic neutropenia with an ANC <0.5×10^9 cells/L documented repeatedly (and confirmed as not varying in a cyclic fashion) for less than six months, ≥12 infections that required	N=6 Mean of 14 months	Primary: Neutrophil response, clinical response, complications, expense comparison Secondary: Not reported	Primary: RhG-CSF 5 µg/kg daily resulted in a mean 44-fold increase (25- to 143-fold increase) in the ANC by the end of the first week of treatment. At 14 months, the minimal rhG-CSF dose requirements ranged from 1 µg/kg once weekly to 5 µg/kg every other day to maintain an ANC >1x10^9 cells/L, but all patients were able to maintain this goal. A significant reduction in the incidence of infections was observed after the initiation of rhG-CSF therapy (P<0.001). A significant reduction in number of days of antibiotic therapy and number of clinical visits was observed after the initiation of rhG-CSF therapy (P<0.001 for both). Low-dose rhG-CSF therapy was well tolerated and no side effects were noted.

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	antibiotic therapy within the previous 12 months, use of prophylactic antibiotics to prevent recurrent infections, one or more life-threatening infections or any combination of these factors, no underlying conditions and availability of medical records			Although not statistically significant, treatment with the lowest effective dose of rhG-CSF demonstrated a total mean annual expense of $4,337 compared to the expense of $12,074 annually prior to rhG-CSF treatment (P=0.09). The mean annual savings per patient was $12,000 ($5,124 to $23,406). Secondary: Not reported
Welte et al[31] RhGM-CSF 3 to 30 µg/kg/day IV for 42 days and subsequently, one to three months later, rhG-CSF 3 to 15 µg/kg/day SC for 142 days All patients were started on 3 µg/kg/day; if no response was seen after 14 days, the dose was increased to the next dose level for 14 days.	T Patients >1 month old with a diagnosis of severe congenital neutropenia, normal kidney and liver function as judged by creatinine, bilirubin, transaminases and coagulation function, normal electrocardiogram, not on	N=5 Duration not specified	Primary: Effects of rhGM-CSF and rhG-CSF on blood cells, maintenance therapy, bone marrow, clinical responses, side effects of treatment Secondary: Not reported	Primary: Treatment with rhGM-CSF increased the ANC count in only one of the five patients in the study (up to 10,296/µL [oscillated between 1,000 and 6,000 cells/µL]). In four patients, the absolute eosinophil count increased from values below 1,000 cells/µL to 3,200 to 5,700 cells/µL. AMC increased two to six fold in four of the five patients as well. Other blood cells such as erythrocytes, platelets or lymphocytes did not change significantly during rhGM-CSF treatment (P values not reported). Treatment with rhG-CSF increased ANC levels to >1,000 cells/µL in all five patients. The absolute eosinophil count was not significantly augmented in all patients (one patient increased fivefold from baseline [oscillation between 100 and 800 cells/µL]). AMC increased two to eight fold in three of the five patients. Four of the five patients maintained an ANC count >1,000 cells/µL during days 43 to 142 of rhG-CSF therapy.

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If after 14 days at the maximal dose no response was observed (no increase in ANC), the therapy was discontinued. All patients also received prophylactic antibiotic therapy with co-trimoxazal, amoxicillin, rifampicin or flucloxacillin.	experimental therapy, chemotherapy, hormonal therapy or immunotherapy, absence of serious infections uncontrolled on antibiotic therapy or requiring white cell transfusion, and absence of anti-neutrophil antibodies			The number of promyelocytes before and during rhGM-CSF treatment did not change significantly in four patients. Two patients in the rhG-CSF showed increases in promyelocytes (2 to 12% and 9 to 12%). All patients' experienced recurrent bacterial and fungal infections prior to rhGM-CSF therapy, and after therapy, no new episodes of severe bacterial infections occurred. Two patients had resolved their infections, one patient had no change and one patient developed Staphylococcus aureus induced paronychia. The one patient who had no change in their infection with rhGM-CSF therapy had their infection resolved within six weeks of rhG-CSF therapy. The other four patients did not experience any bacterial infections during rhG-CSF therapy. Both rhGM-CSF and rhG-CSF were tolerated well by all patients. During the highest dose level of rhGM-CSF treatment (30 µg/kg/day), a mild local phlebitis at the infusion site was observed in all patients. The only serious side effect occurred with rhG-CSF treatment in one patient who suffered from a cutaneous necrotizing vasculitis on both lower legs which resolved with a lowering of the dose. One patient had an increase in serum alkaline phosphatase from 285 U/L before rhG-CSF therapy to 441 units/L after rhG-CSF therapy. The other four patients had no change. Liver and renal functions remained normal. Secondary: Not reported
Delayed or Failed Engraftment in Patients Undergone Allogeneic or Autologous Bone Marrow Transplant				
Weisdorf et al[41] Sargramostim 250 µg/m^2/day SC for 14 days vs	RCT Subjects with graft failure after BMT (failure to achieve a leukocyte count of ≥100 cells/µL by day 21 after	N=47 Duration not specified	Primary: Development of a sustained ANC ≥500 cells/µL for three consecutive days Secondary:	Primary: There was no significant difference in development of a sustained ANC ≥500 cells/µL for three consecutive days between the sargramostim alone group (eight days [two to 61]) and the sequential treatment group (six days [one to 36]; P=0.39). Secondary: There was no significant difference in recovery of red cells to transfusion-

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sargramostim 250 µg/m^2/day SC for 7 days followed by filgrastim 5 µg/kg/day SC for 7 days	transplantation, failure to achieve a leukocyte count ≥300 cells/µL or an ANC ≥200 cells/µL by day 28; or failure to maintain a mean ANC ≥500 cells/µL for 7 days after having previously achieved an ANC ≥500 cells/µL at any time beyond day 28		Recovery of red cells and platelets to transfusion-independence, adverse reactions to cytokine infusions and 100-day survival	independence between the sargramostim alone group (30 days [six to 124]) and the sequential treatment group (42 days [11 to 250]; P=0.24). There was no significant difference in recovery of platelets to transfusion-independence between the sargramostim alone group (28 days [6 to 127]) and the sequential treatment group (42 days [four to 249]; P=0.38). No significant adverse reactions (e.g., fevers, rash, serositis, bone pain) led to discontinuation of either treatments. GVHD was similarly frequent in both treatment arms (P values not reported). Significantly fewer patients died in the sargramostim alone group (one of 23 patients) compared to the sequential treatment group (seven of 24 patients; P=0.026).
Nemunaitis, Singer et al[42] RhGM-CSF 60 to 1,000 µg/m^2/day as a single two-hour IV infusion daily for 14 or 21 days A second course at twice the dose of the first course was allowed if after two weeks from the treatment course, the ANC remained <0.500x10^9 cells/µL and there was no life-threatening toxicity from the rhGM-CSF	DE Patients with malignancy or aplastic anemia who underwent allogeneic, autologous or syngeneic BMT and subsequently developed graft failure	N=37 Duration not specified	Primary: Patient response (ANC ≥500x10^9 cells/µL within 14 days of starting the final course of rhGM-CSF) by type of BMT, effect on infection, effects on GVHD, toxicities and survival Secondary: Not reported	Primary: Nine of 15 patients who underwent an allogeneic BMT increased their ANC to ≥0.500x10^9 cells/µL within 14 days of starting rhGM-CSF. Six patients did not respond to therapy. The mean ANC value in the allogeneic BMT subgroup increased from 0.153±0.140x10^9 cells/µL (zero to 0.360x10^9 cells/µL) at the start of treatment to a mean of 2.545±3.944x10^9 cells/µL (zero to 11.970x10^9 cells/µL) on the last day of the final course (P=0.03). Eleven of the 21 autologous and one syngeneic BMT patient increased their ANC to ≥0.500x10^9 cells/µL within 14 days of starting rhGM-CSF. Ten patients did not respond to therapy. The mean ANC value in the autologous or syngeneic BMT group increased from 0.104±0.130x10^9 cells/µL (zero to 0.472x10^9/L) at start of treatment to 0.964±1.010x10^9 cells/µL (zero to 4.190x10^9 cells/µL) on the last day of the final course of rhGM-CSF (P=0.00047).

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and no evidence of leukemic relapse. A maximum of three courses of rhGM-CSF was administered to each patient.				Fevers (temperature >38°C) were present in 13 of 15 allogeneic BMT patients before treatment with rhGM-CSF. Five patients had bacteremia or fungemia, two had viral infections, and one had liver, spleen, and brain abscesses. Fever was present in 16 of 22 autologous and syngeneic BMT patients before treatment with rhGM-CSF. Five of the 22 patients had bacteremia or fungemia, three had pneumonia and one had a cellulitis. Three patients had graft rejection (only host cells in circulation), two of which responded to rhGM-CSF therapy with recovery of host hematopoiesis. Four patients had only donor hematopoietic cells detected at the time of treatment and all responded to rhGM-CSF. Prior to initiating rhGM-CSF therapy, seven patients had evidence of grade I or II GVHD and none had a GVHD exacerbation. Of the seven patients who received chemically purged autologous marrow, none responded to rhGM-CSF therapy. The four autologous BMT recipients who were administered doses of rhGM-CSF $\geq$500 µg/m^2/day developed myalgias and bone pain during the infusion which resolved within two hours after completion of the rhGM-CSF infusion. At doses $\leq$250 µg/m^2/day, toxicity thought to be associated with rhGM-CSF was observed in one patient who developed sternal and joint pain. In addition, bilirubin increased in three patients and diminished in two others. Overall, 19 patients remained alive after follow-up. The actuarial survival of the 37 patients 100 days and one year after the day they received rhGM-CSF was 59% (95% CI, 44 to 75) and 50% (95% CI, 36 to 60), respectively. Three of the nine allogeneic BMT patients who responded to rhGM-CSF and four of the 12 responders after autologous BMT died. Secondary: Not reported

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Mobilization of Hematopoietic Progenitor Cells into Peripheral Blood Collection by Leukapheresis				
Putkonen et al[43] Filgrastim 5 µg/kg/day SC starting on day 2 post-myeloablative therapy until the end of leukapheresis vs pegfilgrastim 6 to 18 mg once on day 2 post-myeloablative therapy	HC, RETRO Patients with lymphoproliferative malignancies (multiple myeloma, lymphomas and chronic lymphocytic leukemia) requiring stem cell mobilization prior to APBSCT and who had successful mobilization with pegfilgrastim	N=114 Median duration to leuk-apheresis onset was 10 days (10 to 18 days)	Primary: Blood CD34+ cell count at the onset of leukapheresis Secondary: Not reported	Primary: The median blood CD34+ cell count at the onset of leukapheresis was comparable between the filgrastim and pegfilgrastim groups (79x10^6 cells/µL [10 to 390x10^6/L] vs 64x10^6 cells/µL [17 to 805x10^6/L], respectively; P=0.44). The median onset of leukapheresis was similar between the two treatment groups (10 days for both [10 to 18 days for both]; P=0.75). Fifty-three percent of patients in the pegfilgrastim group obtained target yield of CD34+ cells following one leukapheresis cycle, compared to 36% of patients in the filgrastim group (P value not reported). Secondary: Not reported
Weaver et al[44] Filgrastim 5 µg/kg/day SC until PBSC harvests were completed vs sargramostim 250 µg/m^2/day SC until PBSC harvests were completed vs sargramostim 250	MC, OL, RCT Subjects with multiple myeloma, breast cancer or lymphoma	N=156 Duration not specified	Primary: CD34+ cell yields, hematological recovery, morbidity and resource utilization Secondary: Not reported	Primary: Significantly greater CD34+ cells were harvested in the filgrastim alone group (7.1 cells/kg/apheresis [0.03 to 27.00]) and in the sequential dosing group (5.5 cells/kg/apheresis [0.12 to 48.00]) compared to the sargramostim group (2.0 cells/kg/apheresis [0.01 to 31.00]; P=0.0001 and P=0.0002, respectively). ANC recovery was significantly more rapid in those who received filgrastim alone (11 days [zero to 19]) compared to sargramostim alone (14 days [10 to 19]; P=0.001); also the sequential dosing of filgrastim and sargramostim (12 days [10 to 15]) was significant compared to sargramostim alone (P=0.001). Significantly fewer patients had a temperature >38.5° in the filgrastim alone group (9 patients [18%]) and in the sequential dosing group (eight patients [15%]) compared to the sargramostim group (27 patients [52%];

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µg/m^2/day SC for 5 days followed by filgrastim 6 µg/kg/day SC until PBSC harvests were completed Subjects received myelosuppressive chemotherapy with either paclitaxel and cyclophosphamide or etoposide and cyclophosphamide.				P=0.001 for both comparisons). Significantly fewer subjects received IV antibiotics in the filgrastim alone group (12 patients [24%]) and in the sequential dosing group (13 patients [25%]) compared to the sargramostim group (36 patients [69%]; P=0.001 for both comparisons). Significantly fewer subjects had hospital admissions occurred in the filgrastim alone group (10 patients [20%]) and in the sequential dosing group (11 patients [21%]) compared to the sargramostim group (22 patients [42%]; P=0.013 and P=0.017, respectively). Significantly fewer subjects received red blood cells in the filgrastim alone group (11 patients [22%]) compared to the sargramostim group (24 patients [46%]; P=0.008). There were no significant differences between treatment groups in the number of febrile days, number with bacteremia, days of IV antibiotics, days in the hospital, number of receiving platelets and number of days red blood cells were infused. Secondary: Not reported
Reduce Duration of Neutropenia and Neutropenia-Related Sequelae in Patients with Nonmyeloid Malignancies Undergoing Myeloablative Chemotherapy Followed by Marrow Transplantation				
Martino et al[45] Filgrastim 5 µg/kg/day starting on day 5 until neutrophil engraftment vs pegfilgrastim 6 mg once on day 1 post-	RCT Subjects with a de-novo diagnosis of multiple myeloma, stages II to III Durie–Salmon classification	N=37 Duration not specified	Primary: Duration of grade 4 neutropenia (ANC <0.5x10^9/L) Secondary: Incidence of febrile neutropenia (ANC <2x10^9/L and	Primary: There was no significant difference in the duration of grade 4 neutropenia between the pegfilgrastim group (five days [three to 15]) and the filgrastim group (six days [four to 10]; P value not reported). Secondary: The incidence of febrile neutropenia was significantly less in the pegfilgrastim group (61.1%) compared to the filgrastim group (100%; P=0.003).

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transplant All subjects were treated with three cycles of vincristine, adriamycin and dexamethasone, followed by cyclophosphamide and G-CSF and PBCS collection. After PBCS collection, patients received high dose melphalan as the conditioning regimen for the APBSCT.			temperature 38.2°C), duration of febrile neutropenia, duration of fever, incidence of documented infections and platelet engraftment	The duration of febrile neutropenia was significantly less in the pegfilgrastim group (1.5 days [zero to seven]) compared to the filgrastim group (four days [one to nine]; P=0.005). The incidence of fever of unknown origin was significantly less in the pegfilgrastim group (44.0%) compared to the filgrastim group (84.2%; P=0.029). One patient in each of the treatment groups experienced catheter related infections and two patients in each of the treatment groups developed documented infections with positive blood cultures. None of patients developed documented fungal infections. There was no significant difference in mean time to platelet engraftment between the pegfilgrastim group (11 days [nine to 25]) and the filgrastim group (11 days [eight to 22]; P value not reported). Bone pain was the only adverse event considered cytokine related and was reported in 10% of subjects in the pegfilgrastim group and 12% in the filgrastim group (P value not reported).
Castagna et al[46] Filgrastim 5 µg/kg/day SC starting on day 1 post-transplant until ANC recovery to >0.5x10^9/L for two consecutive days vs pegfilgrastim 6 mg SC once on day 1 post-transplant	MC, OL, RCT Adult patients with hematological malignancies and solid tumors who had an adequate harvest of CD34-positive cells (≥3x10^6/kg)	N=80 Duration not specified	Primary: Duration of severe neutropenia (ANC <0.5x10^9/L), number of days to achieve an ANC >0.5x10^9/L starting on day one Secondary: Number of days to achieve an ANC >1x10^9/L starting on day one,	Primary: Pegfilgrastim was not inferior to filgrastim in the duration of severe neutropenia (6.20 vs 5.97 days, respectively; mean difference, 0.23 days; 95% CI, -0.77 to 1.22; P value not reported) and the number of days needed to achieve an ANC >0.5x10^9/L (10.75 vs 11.53 days, respectively; mean difference, -0.78 days; 95% CI, -2.97 to 1.42; P value not reported). Secondary: There was no difference between the filgrastim and pegfilgrastim groups with regard to time to reach ANC >1x10^9/L (12.16 and 11.98 days, respectively; P value not reported) or days with fever (1.63 days and 0.95 days, respectively; P value not reported). The duration of antibiotic therapy was also comparable between the two treatment groups (4.0 days for filgrastim and 5.7 days for pegfilgrastim;

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All patients were treated with high-dose chemotherapy before receiving APBSCT on day 0. The most utilized chemotherapy regimens in the study were carmustine, etoposide, cytarabine and melphalan for lymphomas and high-dose melphalan 200 mg/m^2 for multiple myelomas.			number of days with fever >38ºC, duration of antibiotic and antimycotic therapy, number of documented infections	P=0.152). The result on the number of documented infections was not reported.
Mathew et al[47] Filgrastim 5 µg/kg/day SC starting on day 5 post-transplant vs pegfilgrastim 6 mg SC once on day 1 post-transplant All patients were treated with high-dose chemotherapy before receiving autologous SCT on day 0; regimens differed based on malignancies.	CO, RETRO Adult patients with NHL, HD or multiple myeloma who received an induction chemotherapy followed by autologous SCT	N=164 Mean duration of filgrastim therapy ranged from 5 to 21 days	Primary: Time to neutrophil recovery with ANC ≥0.5x10^9/L once, total days with an ANC <0.5 x 10^9/L, incidence of febrile neutropenia, number of definitive infections, days of IV antibiotic treatment, number of doses of filgrastim and pegfilgrastim given, reported episodes of bone	Primary: The time to neutrophil recovery was 10.9 days with filgrastim and 9.6 days with pegfilgrastim (P<0.0001). The total number of days with an ANC <0.5x10^9/L with filgrastim was 7.6 days and 6.4 days with pegfilgrastim (P<0.001). Pegfilgrastim was associated with fewer incidences of febrile neutropenia compared to filgrastim (59 vs 78%; P=0.012). The mean duration of febrile neutropenia was similar between the two treatment groups (3.2 days for filgrastim and 2.5 days for pegfilgrastim; P=0.08). The filgrastim and pegfilgrastim had similar incidence of definitive infections (32 and 23%, respectively; P=0.294). The duration of IV antibiotic treatment was shorter with pegfilgrastim compared to filgrastim (6.3 vs 9.6 days; P=0.006). Patients in the filgrastim group received an average of nine doses of filgrastim (five to 21 doses), whereas 76 of 82 patients in the pegfilgrastim group received a single dose of pegfilgrastim. Six patients who received

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			pain, incidence of engraftment syndrome Secondary: Not reported	pegfilgrastim also received additional filgrastim. Two patients in the pegfilgrastim group and none in the filgrastim group reported bone pain, while engraftment syndrome occurred in one patient in each group. Secondary: Not reported
Samaras et al[48] Filgrastim 5 µg/kg/day SC starting on day 5 post-transplant until ANC recovery to ≥0.5x10^9/L for three consecutive days vs pegfilgrastim 6 mg SC once on day 1 post-transplant All patients received high-dose carmustine, etoposide, cytarabine and melphalan followed by APBSCT.	RETRO Patients with NHL or HD receiving high-dose BEAM followed by APBSCT	N=54 Duration not specified	Primary: Length of hospital stay, time to engraftment, duration of neutropenia and thrombo-cytopenia, incidence and duration of fever, use of IV antibiotics, need for red blood cell and platelet transfusion during hospital stay	Primary: The length of hospital stay was similar between the filgrastim and pegfilgrastim groups (16.0 vs 16.5 days, respectively; P=0.27). No differences were observed between the filgrastim and pegfilgrastim groups with regard to the time to engraftment (nine days for both; P=0.55), duration of neutropenia (eight vs seven days, respectively; P=0.13) and duration of thrombocytopenia (9.5 vs 7.0 days, respectively; P=0.21). Fever was reported in 80 and 97% of patients in the filgrastim and pegfilgrastim groups, respectively (P=0.057). The duration of fever also appeared similar between the two treatment groups (two days for filgrastim and 4.5 days for pegfilgrastim; P=0.057). Similar percentage of patients in the filgrastim and pegfilgrastim groups received IV antibiotics (90 vs 100%, respectively; P=0.13). The duration of IV antibiotic treatment was also comparable between the two groups (10 days for filgrastim and 11 days for pegfilgrastim; P=0.75). The need for red blood cell and platelet transfusions was similar between the two groups (P=0.27 for red blood cell transfusions; P=0.78 for platelet transfusions).
Samaras et al[49] Filgrastim 5 µg/kg/day SC starting on day 5 post-transplant until	RETRO Patients with multiple myeloma who received	N=72 Median duration of filgrastim use	Primary: Length of hospital stay, time to engraftment, duration of	Primary: Pegfilgrastim had a shorter hospital stay than filgrastim (14.5 days [11 to 47] vs 15.5 days [12 to 64]; P=0.024). The median time to neutrophil engraftment appeared to be faster with

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ANC recovery to ≥0.5x10^9/L for three consecutive days vs pegfilgrastim 6 mg SC once on day 1 post-transplant All patients received high-dose melphalan 200 mg/m^2 followed by APBSCT.	melphalan 200 mg/m^2 followed by APBSCT	was 9 days (3 to 14 days)	neutropenia and thrombo-cytopenia, incidence and duration of fever, use of IV antibiotics, need for red blood cell and platelet transfusion during hospital stay Secondary: Not reported	pegfilgrastim compared to filgrastim (nine days [eight to 18] vs 10 days [eight to 12]; P=0.032). The median duration of neutropenia was also shorter with pegfilgrastim compared to filgrastim (five days [three to 14] vs six days [three to nine]; P=0.0079). The duration of thrombocytopenia was similar between filgrastim and pegfilgrastim (3.0 and 3.5 days, respectively; P=0.39). Seventy-two percent and 63% of patients in the filgrastim and pegfilgrastim groups, respectively, reported incidence of fever (P=0.51). The median duration of fever was similar between the two treatment groups (two days [zero to 12] for filgrastim and one day [zero to 19] for pegfilgrastim; P=0.13). The proportion of patients requiring IV antibiotics were similar in the two treatment groups (89% for filgrastim and 90% for pegfilgrastim; P=0.38). The median duration of treatment was also comparable in filgrastim and pegfilgrastim (six days [zero to 22] and 5.5 days [zero to 36], respectively; P=0.12). There was no difference between the two groups in the need for platelet transfusion (P=0.92); however, more patients in the filgrastim group required platelet transfusions compared to the pegfilgrastim (0.5 [0 to 9] vs 0 [0 to 10]; P=0.00065) Secondary: Not reported
Reducing Time to Neutrophil Recovery and Duration of Fever Following Induction or Consolidation Chemotherapy Treatment of Adults with Acute Myelogenous Leukemia				
Jansen et al[50] Filgrastim 5 µg/kg/day SC from day 0 until neutrophil recovery (ANC >1,500	T Subjects with metastatic (stage IV) or locally advanced (stage	N=46 Duration not specified	Primary: Time to ANC recovery >500 cells/mm^3 and ANC >1,000 cells/mm^3, time to	Primary: Time to ANC recovery >500/mm^3 was significantly faster in the sargramostim group (10.5±1.5 days) compared to the filgrastim group (8.8±1.2 days; P<0.001). In addition, time to ANC recovery >1,000/mm^3 was significantly faster in the sargramostim group (11.0±1.7 days) compared to the filgrastim group (8.9±2.2 days; P=0.001).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cells/mm^3) vs sargramostim 500 µg/kg from day 0 until neutrophil recovery (ANC >1,500 cells/mm^3) Subjects underwent chemotherapy treatment with cyclophosphamide and etoposide and all patients started G-CSF 10 mg/kg/day SC followed by PBSC transplant.	II or III) breast cancer or myeloma who were acceptable candidates for high-dose chemotherapy with PBSC rescue		platelet recovery >20,000 and >50,000, days with growth factor, days with temperature >38.3°C, days of IV antibiotics, number of platelet transfusions and number of red cell units Secondary: Not reported	There were no significant differences in time to platelet recovery >20,000 or >50,000 in the sargramostim group (9.9±1.1, 11.8±2.1 days, respectively) compared to the filgrastim group (11.2±4.7, 14.9±9.3 days, respectively; P=0.40 and P=0.37, respectively). Subjects in the filgrastim group experienced significantly fewer days with growth factor compared to those in the sargramostim (10.8±2.1 vs 12.2±1.5 days; P=0.001). There was no significant difference in the number of days subjects experienced a temperature >38.3°C between the sargramostim and filgrastim groups (2.3±2.4 days vs 1.8±2.1 days; P=0.46). There was no significant difference in the number of days subjects received IV antibiotics between the sargramostim and filgrastim groups (4.3±2.7 vs 4.6±4.3 days; P=0.84). There was no significant difference in the number of platelet transfusions subjects received between the sargramostim and filgrastim groups (2.4±1.7 days vs 3.1±3.2 days; P=0.80). There was no significant difference in the number of red cell units subjects received between the sargramostim and filgrastim groups (2.8±1.6 vs 2.3±2.2; P=0.21). Secondary: Not reported
Shorten Time to Neutrophil Recovery and Reduce Incidence of Infection Following Induction Chemotherapy in Older Adult Patients with Acute Myelogenous Leukemia				
Stone et al[51] GM-CSF 5 µg/kg/day IV given daily until the neutrophil count was at	DB, RCT Patients ≥ 60 years of age with the diagnosis of	N=388 Duration not specified	Primary: Rate of complete remission Secondary:	Primary: There was no significant difference among the rate of complete remission between the GM-CSF group (51%; 95% CI, 44 to 59) and the placebo group (54%; 95% CI, 47 to 61; P=0.61).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
least 1,000 cells/cm^3, there was evidence of the regrowth of leukemia, or severe toxic effects attributable to the study infusion occurred vs placebo given daily until the neutrophil count was at least 1,000/mm^3, there was evidence of the regrowth of leukemia, or severe toxic effects attributable to the study infusion occurred Induction chemotherapy consisted of daunorubicin and cytarabine.	primary AML as defined morphologically by the FAB system of classification		Therapeutic failure, overall survival, duration of neutropenia and duration of hospitalization	Secondary: The reasons for therapeutic failure of remission (i.e., resistant disease or death during marrow hypoplasia) were similar in both treatment groups (P=0.79). The median survival was not significantly different between the two groups (9.4 months; 95% CI, 7.6 to 11.2). The median duration of neutropenia was significantly shorter in the GM-CSF group (15 days; 95% CI, 15 to 1) than in placebo group (17 days; 95% CI, 16 to 19; P=0.02). The median length of hospitalization was not significantly different between the CM-CSF group (28 days; 95% CI, 26 to 31) and the placebo group (30 days; 95% CI, 28 to 33; P=0.11).
Rowe et al[52] Sargramostim 250 µg/m^2 over 4 hours and administered daily until the ANC was >1,500 cells/µL for 3 consecutive days or for a maximum of 42 days	DB, RCT Adult patients >55 but not exceeding 70 years of age with adequate hepatic, renal and cardiac function (bilirubin 52 mg/dL;	N=124 Duration not specified	Primary: Hematologic response (ANC recovery, platelet recovery and red blood cell recovery) and rate of complete remission	Primary: The median time to ANC recovery was significantly shorter in the sargramostim group compared to the placebo group. Median time to ANC recovery of >500 cells/µL in the sargramostim group was 13 days compared to 17 days for the placebo group (P=0.001) and the median time to ANC recovery of >1,000 cells/µL was 14 vs 21 days, respectively (P=0.001). There was no significant differences between the sargramostim and placebo groups in median recovery rates of platelets (11 vs 12 days,

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Induction consisted of standard daunorubicin and cytarabine.	creatinine <2 mg/dL; and normal cardiac left ventricular ejection fraction), no previous cytotoxic or radiation therapy, morphologic proof of AML, no known antecedent myelody-splasiacytogenetic and immunophenotypic analysis performed on prestudy specimens		Secondary: Treatment-related toxicity, infectious toxicity and median survival	respectively; P=0.11) and red blood cells (13 vs 14 days, respectively; P=0.39). There were significantly more patients who experienced complete remission in the sargramostim group (36 patients [60%]) compared to the placebo group (25 patients [45%]; P=0.08). Secondary: The treatment-related mortality was not significantly different between the sargramostim group (three patients [6%]) compared to the placebo group (seven patients [15%]; P=0.18). There were no differences between the groups for any other toxicities, including weight gain (8% on sargramostim and 21% on placebo), cardiac events, or pulmonary events, and no patient withdrew from study drug because of toxicity or leukemia regrowth. Grade 4 and 5 infections occurred significantly less in the sargramostim group (five patients [10%]) compared to the placebo group (17 patients [36%]; P=0.002); however there was no significant difference in occurrence of the combination of grade 3, 4 and 5 infections (27 [52%] vs 33 patients [70%], respectively; P=0.068). Death associated with pneumonia occurred significantly less in the sargramostim group (two patients [14%]) compared to the placebo group (seven patients [54%]; P=0.046). The median survival time was significantly longer in the sargramostim group (10.6 months) compared to the placebo group (4.8 months; P=0.048).
Büchner et al[53] Sargramostim 250 µg/m^2/day continuous IV infusion started on	HC Adult patients at all ages with early relapse occurring	N=92 Duration not specified	Primary: Complete remission rate Secondary:	Primary: There was no statistical difference among complete remission rates between the sargramostim group (18 patients [50%]) and the control group (18 patients [32%]; P=0.09).

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
day 4 vs control group (sequential patients treated by the identical chemotherapy at the same situations) Early or multiple relapses were treated with one course S-HAM and newly diagnosed AML and AML late relapses in the higher age group were treated with TAD9.	in the first 6 months of remission and with multiple relapse, and patients ≥65 years with newly diagnosed AML or late relapse		Death rate, definite nonresponse rate, adverse events, duration of remission	Secondary: The sargramostim group had significantly fewer early (within six weeks) deaths (five patients [14%]) compared to the control group (22 patients [39%]; P=0.009); however there was no significant difference among later hypoplastic deaths between the two groups (seven [19%] vs seven patients [13%]; P not reported). There was no significant difference in the number of definite nonresponders between the sargramostim group (six patients [17%]) and the control group (nine patients [16%]; P value not reported). The sargramostim group showed a higher overall frequency, including all grades of decrease in serum protein (P=0.02), prothrombin (P=0.02) and pseudo-cholinesterase levels (P=0.008). In the control group, elevation of serum transaminases was more frequent overall (P=0.008) and in lower-grade elevations and showed more frequent cardiac events (P=0.018). Remission duration does not seem to be reduced after GM-CSF compared to the control group (P value not reported).

Drug regimen abbreviations: IV=intravenous, SC=subcutaneous
Study abbreviations: CO=cohort, DB=double blind, DE=dose-escalation, ES=extension study, HC=historical control, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observation study, PC=placebo controlled, RCT=randomized controlled trial, RETRO=retrospective, T=trial, XO=crossover
Miscellaneous abbreviations: ALL=acute lymphocytic leukemia, AMC=absolute monocytes count, AML=acute myelogenous leukemia, ANC=absolute neutrophil count, APBSCT=autologous peripheral blood stem cell transplantation, BEAM= carmustine, etoposide, cytarabine, melphalan, BMT=bone marrow transplant, CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone, CI=confidence interval, CSF=colony-stimulating factor, ECOG=Eastern Cooperative Oncology Group, FAB=French-American-British, G-CSF=granulocyte-colony-stimulating factor, GM-CSF=granulocyte-macrophage-colony stimulating factor, GVHD=graft-versus-host disease, IPI=international prognostic index, HD=Hodgkin's disease, HLA=human leukocyte antigen, NHL=non-Hodgkin's lymphoma, OR=odds ratio, PBC=peripheral blood count, PBSC=peripheral blood stem cell, PBSCT=peripheral blood stem cell transplant, rhG-CSF=recombinant human granulocyte colony-stimulating factor, rhGM-CSF=recombinant human granulocyte-macrophage colony-stimulating factor, RR=relative risk, SCT=stem cell transplant, SD=standard deviation, S-HAM=sequential high-dose cytosine arabinoside and mitoxantrone,TAD9=9-day 6-thioguanine with cytosine arabinoside and daunorubicin, WBC=white blood cell, WHO=World Health Organization

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Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Filgrastim	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. FDA-approved for use in pediatric patients.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
Filgrastim-sndz	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. FDA-approved for use in pediatric patients.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
Pegfilgrastim	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use with caution.
Sargramostim	Safety and efficacy in elderly patients have not been established.* Safety and effectiveness in pediatric patients have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown; use with caution.

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Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Tbo-Filgrastim	No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Safety and effectiveness in pediatric patients have not been established.	No dosage adjustment required for creatinine clearance ≥60 mL/min. Not studied in patients with creatinine clearance <60 mL/min.	Not studied in hepatic dysfunction.	C	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events[1-5]

Adverse Event	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-Filgrastim
Cardiovascular System					
Cardiac	-	-	-	23	-
Hemorrhage	-	-	-	23 to 29	-
Hypertension	-	-	-	25 to 34	-
Hypotension	-	-	-	13	-
Tachycardia	-	-	-	11	-
Central Nervous System					
Anxiety	-	-	-	11	-
Central nervous system disorder	-	-	-	11	-
Chills	-	-	-	19 to 25	-
Fatigue	11	11	-	-	-
Fever	12	12	-	77 to 96	-
Headache	-	-	16	36	a
Insomnia	-	-	-	11	-
Neuro-clinical	-	-	-	42	-
Neuro-motor	-	-	-	25	-
Neuro-psych	-	-	-	15	-
Neutropenic fever	13	13	-	-	-
Paresthesia	-	-	-	11	-
Pyrexia	-	-	23	-	-
Dermatological					
Alopecia	18	18	48	37 to 73	-
Pruritus	-	-	-	23	-
Rash	-	-	-	44 to 70	-
Skin	-	-	-	77	-

Adverse Event	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-Filgrastim
Sweet's Syndrome	-	-	-	-	a
Gastrointestinal					
Abdominal pain	-	-	-	38	-
Anorexia	-	-	-	13 to 54	-
Constipation	-	-	10	-	-
Diarrhea	14	14	29	52 to 89	-
Dyspepsia	-	-	-	17	-
Dysphagia	-	-	-	11	-
Gastrointestinal disorder	-	-	-	37	-
Gastrointestinal hemorrhage	-	-	-	11 to 27	-
Hematemesis	-	-	-	13	-
Mucositis	12	12	-	-	-
Nausea/vomiting	57	57	13	46 to 90	a
Stomatitis	-	-	-	24 to 62	-
Laboratory Test Abnormalities					
Bilirubinemia	-	-	-	30	-
Blood dyscrasia	-	-	-	25	-
Coagulation	-	-	-	19	-
High blood urea nitrogen	-	-	-	23	-
High cholesterol	-	-	-	17	-
Hyperglycemia	-	-	-	25 to 41	-
Hypomagnesemia	-	-	-	15	-
Increased creatinine	-	-	-	15	-
Increased serum glutamic pyruvic transaminase	-	-	-	13	-
Leukopenia	-	-	-	17	-
Liver damage	-	-	-	13	-
Low albumin	-	-	-	27	-
Thrombocytopenia	-	-	-	19	a
Respiratory					
Dyspnea	-	-	-	15 to 28	-
Epistaxis	-	-	-	17	-
Lung disorder	-	-	-	20	-
Pharyngitis	-	-	-	23	-
Pulmonary	-	-	-	48	-
Rhinitis	-	-	-	11	-
Other					
Allergy	-	-	-	12	-
Arthralgia	-	-	16	11	-
Asthenia	-	-	13	17 to 66	-
Bone pain	-	-	31	21	3.4
Chest pain	-	-	-	15	-
Cutaneous vasculitis	-	-	-	-	a
Edema	-	-	-	13 to 34	-

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Adverse Event	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-Filgrastim
Eye hemorrhage	-	-	-	11	-
Infection	-	-	-	65	-
Liver	-	-	-	77	-
Malaise	-	-	-	57	-
Metabolic	-	-	-	58	-
Mucous membrane disorder	-	-	-	75	-
Myalgia	-	-	21	-	a
Pain	-	-	-	17	-
Peripheral edema	-	-	12	11 to 15	-
Sepsis	-	-	-	11	-
Skeletal pain	22	-	-	-	-
Urinary tract disorder	-	-	-	14	-
Weight loss	-	-	-	27	-

- Event not reported or incidence ≤10%.
a Rate not reported

Contraindications

Table 7. Contraindications[1-5]

Contraindication	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-Filgrastim
Concurrent use with chemotherapy and radiotherapy.				a	
Neonatal use				a	
Excessive leukemic myeloid blasts in the bone marrow or peripheral blood (≥10%)				a	
Known hypersensitivity to acrylic			a		
Know hypersensitivity to human granulocyte colony-stimulating factors or any component.	a	a	a	a	a
Known hypersensitivity to yeast-derived products.				a	

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Warnings/Precautions

Table 8. Warnings and Precautions[1-5]

Warnings and Precautions	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-Filgrastim
Acute Respiratory Distress Syndrome (ARDS) has been reported. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue use in patients with ARDS.	a	a	a	a	a
Allergy to Acrylics; the injection device uses acrylic adhesives; serous allergic reactions may occur in patients allergic to acrylic.			a		
Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in peripheral blood progenitor cell collection mobilization.	a	a			
Benzyl Alcohol is a constituent and is associated with “Gasping Syndrome” in premature infants. Do not administer to neonates				a	
Capillary leak syndrome has been reported after G-CSF administration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Closely monitor and provide standard symptomatic treatment, which may include intensive care.	a	a		a	a
Cardiovascular symptoms of transient supraventricular arrhythmia have been reported, particularly in patients with a history of arrhythmia. Use with caution in patients with preexisting cardiac disease.				a	
Cutaneous Vasculitis has been reported; hold therapy and restart with a reduced dose when symptoms resolve and ANC has decreased.	a	a			
Leukocytosis; Discontinue use if white blood cell count >10,000/mm^3 in patients with cancer receiving myelosuppressive chemotherapy.	a	a			
Leukocytosis; Discontinue use if white blood cell count >100,000/mm^3 if being used for peripheral blood progenitor cell collection and therapy.	a	a			
Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated for severe chronic neutropenia (SCN). Confirm the diagnosis of SCN before initiating therapy.	a	a			
Nuclear Imaging; transient positive bone-imaging changes have been associated with use; considerations should be made when interpreting bone-imaging results.	a	a			
Potential Effect on Malignant Cells; may act as a growth factor in tumor cells; safety and efficacy in chronic myeloid leukemia and myelodysplasia has not been established.	a	a	a		a
Renal and Hepatic Dysfunction; in patients with preexisting renal or hepatic dysfunction increases in serum creatinine, bilirubin, or hepatic enzymes have been reported. Dose reduction has resulted in a decrease to pre-treatment levels. Monitor patients with preexisting dysfunction at least every other week during therapy.				a	
Serious allergic reactions, including anaphylaxis, have been reported; can recur within days after the discontinuation of allergy treatment. Permanently discontinue in patients with serious allergic reactions.	a	a	a		a

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Warnings and Precautions	Filgrastim	Filgrastim-sndz	Pegfilgrastim	Sargramostim	Tbo-Filgrastim
Sickle cell crisis has been reported in patients with sickle cell trait or sickle cell disease.	a	a	a		a
Simultaneous use with chemotherapy and radiation therapy is not recommended. Do not administer within 24 hours before and after administration of cytotoxic chemotherapy. Avoid simultaneous use with radiation. Safety and efficacy with simultaneous use has not been established for chemotherapy or radiation.	a	a			
Splenic rupture has been reported. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or rupture.	a	a	a		a
Thrombocytopenia has been reported. Monitor platelet counts.	a	a			

Drug Interactions

There are no specific drug interactions reported with the use of granulocyte colony-stimulating factors and associated agents.[1-5] It is recommended to use caution when granulocyte colony-stimulating factor agents are used in combination with other agents which may potentiate the release of neutrophils, such as lithium and corticosteroids.[1-5]

Dosage and Administration

Table 9. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Filgrastim	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies and Induction and/or Consolidation Chemotherapy for AML: Vial, prefilled syringe: initial, 5 µg/kg/day via SC, short IV infusion (15 to 30 minutes), or continuous IV infusion daily; maintenance, increase dose by 5 µg /kg for each chemotherapy cycle based on ANC Myeloablative chemotherapy followed by BMT: Vial, prefilled syringe: initial, 10 µg/kg/day via IV infusion (over <24 hours) daily; maintenance, titrate dose based on neutrophil response Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Vial, prefilled syringe: 10 µg/kg/day SC for at least four days before leukapheresis and continue until the last leukapheresis.	Refer to adult dosing.	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL

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Generic Name	Adult Dose	Pediatric Dose	Availability
	Congenital Neutropenia: Vial, prefilled syringe: initial, 6 µg/kg SC twice daily; maintenance, dose should be individualized; maximum, doses up to 100 µg/kg/day have been required rarely. Idiopathic or Cyclic Neutropenia: Vial, prefilled syringe: initial, 5 µg/kg SC daily; maintenance, dose should be individualized. Hematopoietic Syndrome of Acute Radiation Syndrome: Vial, prefilled syringe: initial, 10 µg/kg SC daily as soon as possible after confirmed exposure to radiation doses greater than 2 gray (Gy) until ANC >1,000 mm^3 for three consecutive CBCs obtained approximately every three days or ANC>10,000 mm^3 after radiation-induced nadir.		
Filgrastim-sndz	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies and Induction and/or Consolidation Chemotherapy for AML: Vial, prefilled syringe: initial, 5 µg/kg/day via SC, short IV infusion (15 to 30 minutes), or continuous IV infusion daily; maintenance, increase dose by 5 µg /kg for each chemotherapy cycle based on ANC Myeloablative chemotherapy followed by BMT: Vial, prefilled syringe: initial, 10 µg/kg/day via IV infusion (over <24 hours) daily; maintenance, titrate dose based on neutrophil response Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Vial, prefilled syringe: 10 µg/kg/day SC for at least four days before leukapheresis and continue until the last leukapheresis. Congenital Neutropenia: Vial, prefilled syringe: initial, 6 µg/kg SC twice daily; maintenance, dose should be individualized; maximum, doses up to 100 µg/kg/day have been required rarely. Idiopathic or Cyclic Neutropenia: Vial, prefilled syringe: initial, 5 µg/kg SC daily; maintenance, dose should be	Refer to adult dosing.	Vial: 300 µg/1 mL 480 µg/1.6 mL Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL

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Generic Name	Adult Dose	Pediatric Dose	Availability
	individualized.		
Pegfilgrastim	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies: Prefilled syringe: 6 mg SC once per chemotherapy cycle.	Safety and efficacy have not been established in pediatric patients.	Prefilled Syringe: 6 mg/0.6 mL
Sargramostim	Induction Chemotherapy for AML: Vial (powder, solution): 250 µg/m^2/day IV over four hours daily starting approximately on day 11 or four days following the completion of induction chemotherapy until ANC>1,500 mm^3 for three consecutive days or a maximum of 42 days. If a second cycle of chemotherapy is required, administer approximately four days after the completion of chemotherapy. Non-Hodgkin's lymphoma, acute lymphoblastic leukemia and Hodgkin's disease undergoing autologous BMT: Vial: 250 µg/m^2/day IV beginning two to four hours after bone marrow infusion and not less than 24 hours after the last dose of chemotherapy or radiotherapy and continued until absolute neutrophil count >1,500 cells/mm3 for three consecutive days Allogeneic or autologous bone marrow transplantation in whom engraftment is delayed or has failed: Vial: initial, 250 µg/m^2/day IV for 14 days; treatment may be repeated after seven days off therapy; if a third course is necessary, dose is increased to 500 µg/m^2/day. Autologous Peripheral Blood Progenitor Cell Collection and Therapy: Vial (powder, solution): 250 µg/m^2/day IV over 24 hours or SC once daily, The optimal schedule for collection has not been established. Immediately following infusion of progenitor cells, give 250 µg/m^2/day IV over 24 hours or SC once daily and continue until ANC>1,500 cells/mm^3 for three consecutive days.	Safety and efficacy have not been established in pediatric patients.	Vial (powder for reconstitution): 250 µg Vial (solution) 500 µg/1 mL
Tbo-Filgrastim	Severe neutropenia in patients receiving myelosuppressive therapy for nonmyeloid malignancies: Prefilled syringe: 5 µg/kg SC daily until the expected neutrophil nadir is passed and neutrophil count has recovered to the	Safety and efficacy have not been established in pediatric patients.	Prefilled Syringe: 300 µg/0.5 mL 480 µg/0.8 mL

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Generic Name	Adult Dose	Pediatric Dose	Availability
	normal range.		

AML=acute myeloid leukemia, ANC=absolute neutrophil count, BMT=bone marrow transplant, IV=intravenous, SC=subcutaneous

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
National Comprehensive Cancer Network: **Myeloid Growth Factors Clinical Practice Guidelines in Oncology (2010)**[11]	Prophylactic use of colony-stimulating factors (CSFs) · For patients at high risk of febrile neutropenia, prophylactic CSFs is recommended if the risk of febrile neutropenia is 20% or greater and for any patient considered at high risk, regardless of whether the treatment is intended to be curative, to prolong survival or to manage symptoms. · Patients at intermediate risk of febrile neutropenia: o Intermediate risk is defined as a 10 to 20% probability of developing febrile neutropenia or a neutropenic event that would compromise treatment. o Whether the treatment is intended to be curative, to prolong survival or to manage symptoms, it is recommended that individualized consideration of CSF therapy be based on physician-patient discussion of the risk-benefit ratio of the likelihood of developing febrile neutropenia, the potential consequences of a neutropenic event and the implications of reduced chemotherapy doses. o If patient risk factors determine the risk, CSF is a reasonable prophylactic option. o If the risk is due to the chemotherapy regimen and the treatment is intended to prolong survival or to manage symptoms, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored. · Patients at low risk of febrile neutropenia: o In patients at low risk of febrile neutropenia, defined as <10% risk, routine use of CSFs is not considered cost-effective, and alternative treatment options are appropriate. o CSFs may be considered if the patient is receiving curative or adjuvant treatment and is at significant risk for serious medical consequences of febrile neutropenia, including death. · Evaluation of subsequent chemotherapy cycles: o Patient evaluation should occur prior to each subsequent chemotherapy cycle to determine the risk categorization and treatment intent. o If a patient experiences an episode of febrile neutropenia or a dose-limiting neutropenic event despite receiving CSF therapy, it is recommended that a chemotherapy dose reduction or change in treatment regimen occurs unless there is an impact on patient survival. · Chemotherapy regimens and risk of febrile neutropenia: o CSF prophylaxis is recommended when using a chemotherapy regimen with an incidence of >20% of febrile neutropenia. o Benefits of pegfilgrastim have not been shown in regimens given under two week duration; therefore, it should be avoided in

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Clinical Guideline	Recommendations
	patients receiving weekly chemotherapy. Therapeutic uses of CSFs · Patients with febrile neutropenia who are receiving prophylactic filgrastim or sargramostim should continue with CSF therapy. However, since pegfilgrastim is long-acting, those who have received prophylaxis with pegfilgrastim should not be treated with an additional CSF. · Due to the lack of evidence supporting the therapeutic use of pegfilgrastim, only filgrastim and sargramostim should be used in this therapeutic setting. · It is recommended for those who have not received prophylactic CSFs to be evaluated for risk factors for infection-related complications or poor clinical outcome. These include: old age (>65 years), sepsis syndrome, severe (absolute neutrophil count [ANC] <100 cells/μL) or anticipated prolonged (>10 days) neutropenia, pneumonia, invasive fungal infection or other clinically-documented infections. If risk factors are present, CSFs should be considered. Dosing and administration · Based on available data regarding the CSFs in prophylaxis of febrile neutropenia, when choosing among the myeloid growth factors, filgrastim and pegfilgrastim are considered to have more evidence than sargramostim. · Initial doses of filgrastim are started at a daily dose of 5 μg/kg beginning within one to three days after completion of chemotherapy until post-nadir ANC recovery to normal or near-normal ANC levels by laboratory standards. · There is evidence to support the use of pegfilgrastim 24 hours after completion of chemotherapy given every three weeks in one dose of 6 mg per cycle of treatment. · Administration of filgrastim or pegfilgrastim within 24 hours after completion of chemotherapy is not recommended. · There is insufficient evidence to support a strong recommendation for sargramostim in nonmyeloid malignancies. · Subcutaneous administration is preferred for filgrastim, pegfilgrastim and sargramostim. Severe chronic neutropenia · Granulocyte CSF (G-CSF) is an established effective treatment for cyclic, congenital and idiopathic neutropenia.
The American Society of Clinical Oncology: **2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-based Clinical Practice Guideline (2006)**[12]	· Reduction in febrile neutropenia is an important clinical outcome that justifies the use of CSFs, regardless of their impact on other factors, when the risk of febrile neutropenia is approximately 20% and no other equally effective regimen that does not require CSFs is available. Primary prophylactic CSF administration (first and subsequent-cycle use) · Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients who have a high risk of febrile neutropenia based on age, medical history, disease characteristics and myelotoxicity of the chemotherapy regimen. · For “dose dense” regimens, CSFs are required and recommended. · The standard of care is to use chemotherapy regimens that do not require CSFs because of equal efficacy and lower risk of febrile neutropenia if such regimens are available. · Current data demonstrates effectiveness and supports the use of CSFs

Clinical Guideline	Recommendations
	when regimens that have a febrile neutropenia incidence of >20% are used; therefore, this practice is recommended. Secondary prophylactic CSF administration · Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. Therapeutic use of CSF · CSFs should not be routinely used for patients with neutropenia who are afebrile. · CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with febrile neutropenia. However, CSFs should be considered in patients with febrile neutropenia who are at high-risk for infection associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. Use of CSFs to increase chemotherapy dose-intensity and dose-density · Use of CSFs allows a modest to moderate increase in dose density and/or dose-intensity of chemotherapy regimens. · A survival benefit is suggested by the current data when CSFs are used with dose-dense regimens in specific settings (e.g., node-positive breast cancer and possibly non-Hodgkin's lymphoma [NHL]), but this data cannot be applied to other diseases. · It is recommended to only use dose dense regimens within an appropriately designed clinical trial or when use is supported by convincing efficacy data. Use of CSFs as adjuncts to progenitor-cell transplantation · The current standard of care is the administration of CSFs to mobilize peripheral-blood progenitor cell (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplantation. Use of CSFs in patients with acute leukemia and myelodysplastic syndromes · For acute myeloid leukemia (AML), CSF use following initial induction therapy is reasonable, as studies have demonstrated a decrease in neutropenia duration, although there has been no favorable impact on remission rate, remission duration or survival. Patients older than 55 years of age may be most likely to benefit from CSF use. · For priming of leukemia cells in patients with AML, use of CSFs is not recommended. · After the completion of consolidation chemotherapy, CSF use can be recommended to possibly decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive post-remission chemotherapy. · Due to the lack of information regarding pegylated CSFs in patients with myeloid leukemia, it is recommended that they not be used in such patients outside of clinical trials. · For myelodysplastic syndromes, intermittent administration of CSFs may be considered in certain patients with severe neutropenia and recurrent infection; however, there is a lack of data supporting the routine long-term

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	continuous use of CSFs in these patients. · For acute lymphocytic leukemia (ALL), to reduce the duration of neutropenia, CSFs are recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post remission course. · For acute leukemia in relapse it is recommended that CSFs be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia due to the lack of expected response. Use of CSFs in patients receiving radiotherapy with or without concurrent chemotherapy · In those patients who are expected to have prolonged delays in radiation treatment due to neutropenia and are not receiving chemotherapy, CSFs may be considered. · In those patients receiving concurrent chemotherapy and radiation of the mediastinum, CSFs should be avoided. Use of CSFs in older patients · To reduce the incidence of febrile neutropenia and infections, prophylactic CSFs should be given to patients 65 years of age and older with diffuse aggressive lymphoma treated with curative chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] or more aggressive regimens). Use of CSFs in the pediatric population · The use of CSFs in pediatric patients will almost always be guided by clinical protocols. The use of CSFs is reasonable for the primary prophylaxis of pediatric patients with a likelihood of febrile neutropenia. · The use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients. · Due to the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with CSFs, their use represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the use of CSFs in children with ALL should be considered with caution. CSF initiation, duration, dosing and administration · CSFs should be given 24 to 72 hours after the administration of myelotoxic chemotherapy and should be continued until the ANC reaches at least 2 to $3x10^9$ cells/L. · For PBPC mobilization, CSFs should be started at least four days before the first leukapheresis procedure and continued until the last leukapheresis. · In adults, the recommended CSF doses are 5 µg/kg/day for G-CSF and 250 $µg/m^2$/day for granulocyte macrophage CSF (GM-CSF) for all clinical settings other than PBPC mobilization. · In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 µg/kg/day maybe preferable. · The preferred route of CSF administration is subcutaneous. Pegylated G-CSF initiation, duration, dosing and administration · Pegfilgrastim 6 mg should be given once 24 hours after completion of chemotherapy. · The 6 mg formulation should not be used in infants, children or small

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	adolescents weighing less than 45 kg. Special comments on comparative clinical activity of G-CSF and GM-CSF · No guideline recommendation can be made regarding the equivalency of the two CFSs. · Further trials are recommended to study the comparative clinical activity, toxicity and cost-effectiveness of G-CSF and GM-CSF. Special comments on growth factors as a treatment for radiation injury · Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.
European Organization for Research and Treatment of Cancer: **2010 Update of European Organization for Research and Treatment of Cancer Guidelines for the Use of Granulocyte-Colony Stimulating Factor to Reduce the Incidence of Chemotherapy-Induced Febrile Neutropenia in Adult Patients with Lymphoproliferative Disorders and Solid Tumors (2010)**[14]	Patient-related risk factors for increased risk of febrile neutropenia · Prevention of chemotherapy-induced febrile neutropenia should be considered a clinical priority. · Prior to administering each cycle of chemotherapy, evaluation of patient-related risk factors should be included in the overall assessment. · Other risk factors that should be evaluated for include: elderly age (aged 65 and over), advanced stage of disease, experience of previous episode(s) of febrile neutropenia, lack of G-CSF use and lack of antibiotic prophylaxis. · Indiscriminate use of antibiotic prophylaxis is not recommended. Chemotherapy regimens associated with increased risk of febrile neutropenia · Chemotherapy regimens are categorized based on their potential to cause febrile neutropenia (>20%, 10 to 20%, <10%); therefore, this risk should be taken into consideration when using certain chemotherapy regimens. G-CSF to support chemotherapy · G-CSF prophylaxis should be used as supportive treatment in cases when dose-dense or dose-intense chemotherapy regimens have demonstrated survival benefits. · G-CSF should be used as primary prophylaxis to maintain a chemotherapy regimen if dose or intensity reduction has demonstrated poor prognosis when the treatment is potentially curative or intended to prolong survival. · When the treatment is palliative, the use of less myelosuppressive chemotherapy or dose/schedule modification should be considered. Impact of the overall febrile neutropenia risk on G-CSF use · At the beginning of each cycle, each patient should be individually assessed for the risk of complication related to febrile neutropenia which should include patient-related risk factors, the chemotherapy regimen and associated complications and treatment intent. · Prophylactic G-CSF therapy is recommended in patients whose overall risk of febrile neutropenia is >20%. · When a chemotherapy regimen associated with a febrile neutropenia risk of 10 to 20% is used, patient characteristics should be taken into account when reviewing the overall risk of febrile neutropenia. G-CSF in patients with existing febrile neutropenia · G-CSF treatment in patients with solid tumors and malignant lymphoma should be reserved for those patients who are not responding to appropriate

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	antibiotic management and who are developing life-threatening infections (such as severe sepsis or septic shock). Choice of formulation · Where indicated, filgrastim, lenograstim* and pegfilgrastim are all recommended to prevent febrile neutropenia and febrile neutropenia related complications due to their clinical efficacy and studies demonstrating comparable efficacy.
British Committee for Standards in Hematology: **Guidelines on the Use of Colony-stimulating Factors in Hematological Malignancies (2003)**[54]	· Due to the lack of comparative trials and clinical trial data, there seems to be no evidence demonstrating efficacy or outcome differences between the G-CSF and GM-CSF products when administered at recommended doses. These guidelines do not differentiate between the agents. Prophylactic and adjunctive use · Primary prophylaxis is not routinely recommended unless the expected incidence of febrile neutropenia is >40%. · Secondary prophylaxis cannot be routinely justified because of a lack of available evidence but is indicated for tumors in which dose reduction or dose delay would compromise overall survival. · Adjunctive treatment is not recommended for patients with uncomplicated febrile neutropenia but should be considered in patients with poor prognostic factors. Use of CSFs in association with chemotherapy · AML: The routine use of CSF is recommended after consolidation chemotherapy. CSF is recommended after induction if it is appropriate to reduce hospital stay or antibiotic usage. · ALL: G-CSF is indicated to reduce the severity of neutropenia following intensive phases of therapy. · Myelodysplastic syndromes: CSFs are indicted to reduce the severity of neutropenia in patients receiving intensive chemotherapy. CSFs are also recommended on an intermittent basis for patients with neutropenia and infection, but continuous prophylactic use is not routinely justified. · Aplastic anemia: There is insufficient evidence to make any general recommendations. Hence patients should be given CSFs only on an individual therapeutic trial basis. · Bone marrow failure syndromes: G-CSF is recommended when improvement of neutrophil count is appropriate. · Malignant lymphomas: There is evidence to support the routine use of CSFs to reduce the incidence of infection, chemotherapy delay and hospitalization, especially when the risk of febrile neutropenia exceeds 40%. There is also emerging evidence of improved survival with G-CSF-supported dose intensification in elderly patients with high-grade NHL. At present, this evidence is insufficient to justify a change in policy in all patients with lymphoma, but elderly patients may benefit from G-CSF support. CSFs for PBPC mobilization · CSFs are indicated for the mobilization of PBPCs. CSFs after PBSC and marrow transplantation · CSFs are indicated to accelerate reconstitution after allogeneic and autologous PBPC transplantation or bone marrow transplant.

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National Comprehensive Cancer Network: **Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (2011)**[13]	Monitoring and supportive care · Growth factor support may be considered in the elderly once chemotherapy is complete. · Recommendations regarding the use of cytokines for infection or for slow marrow recovery are left to institutional policy. · G-CSF or GM-CSF should be discontinued for a minimum of seven days before obtaining bone marrow to document remission as CSF therapy may confound interpretation of the bone marrow. · Growth factors should not be used in patients with acute promyelocytic leukemia.
British Committee for Standards in Hematology: **Guidelines on the Management of Acute Myeloid Leukemia in Adults (2006)**[55]	Growth factors · Growth factors following AML chemotherapy have shown no survival benefit but have demonstrated reduction in the duration of neutropenia, antibiotic use and hospital stay. · The cost-benefit advantages of routine growth factor use are uncertain. · G-CSF is recommended after induction if it is appropriate to reduce hospital stay or antibiotic usage. · The routine use of growth factor therapy in AML is not recommended. Standard chemotherapy · There is insufficient evidence to support routine use of G-CSF or GM-CSF with induction chemotherapy in patients over 60 years of age, although this may be appropriate if it is desirable to reduce hospitalization or antibiotic usage. Management of AML in patients who are pregnant · Pregnant patients with other forms of AML, other than promyelocytic leukemia-retinoic acid receptor-positive acute promyelocytic leukemia, and with stable disease may defer chemotherapy and be supported with growth factors and blood products until delivery can be safely induced at about 30 weeks.
National Comprehensive Cancer Network: **Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (2011)**[56]	Supportive care · Use of G-CSF or GM-CSF is not recommended for routine infection prophylaxis. · Use of G-CSF or GM-CSF may be considered in a neutropenic patient who has recurrent or resistant infections. · Low-dose G-CSF or GM-CSF may be combined with recombinant human erythropoietin for anemia when indicated, particularly in patients who are not responding to erythropoiesis-stimulating agents and have serum erythropoietin level of 500 mUnits/mL or less.
United Kingdom Myelodysplastic Syndromes Guideline Group: **Guidelines for the Diagnosis and Therapy of Adult Myelodysplastic Syndromes (2003)**[57]	Erythropoietin with or without G-CSF · Many studies have clearly demonstrated that erythropoietin±G-CSF can increase hemoglobin levels and reduce or eliminate red blood cell transfusion in selected myelodysplastic syndromes patients. · It is recommended that patients with refractory anemia and refractory anemia with excess blasts who are not eligible for chemotherapy or stem cell transplantation and are symptomatic of anemia, with no or low transfusion requirement (<2 units/month) and a baseline erythropoietin level <200 units/L who have not responded to a trial of erythropoietin alone for six weeks be considered for daily G-CSF therapy, doubling the dose of erythropoietin or both for six more weeks. The G-CSF dose should be doubled weekly (e.g., 75 µg to 150 µg then to 300 µg) to maintain the white

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	blood cell between 6 and $10x10^9$ cells/L. In patients who respond, once the maximum response has been reached, the G-CSF can be reduced to thrice weekly, and the erythropoietin dose can be reduced by one day a week at four weekly intervals (e.g., five days a week to four days then three days) to the lowest dose that retains response. · It is recommended that the combination of erythropoietin and G-CSF be used from the beginning for patients with refractory anemia with excess blasts, symptomatic anemia, baseline erythropoietin levels <500 units/L and a transfusion requirement <2 units/month. · Due to the lack of published data, it is encouraged to continue randomized-controlled trials of erythropoietin±G-CSF to address the issues of quality of life, survival advantage and pharmacoeconomics. Prophylactic management of infection · Prophylactic low-dose G-CSF therapy may be considered in patients who are severely neutropenic in order to maintain a neutrophil count >$1X10^9$ cells/L.

Conclusions

Colony-stimulating factors (CSFs) are growth factors which stimulate the production and enhance recovery of neutrophils.[58] There are currently two types of CSFs available in the United States, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Filgrastim, filgrastim-sndz, tbo-filgrastim and pegfilgrastim are the currently available G-CSFs.[1-3,5] Filgratstim-sndz is considered a biosimilar drug to parent molecule filgrastim; however, due to regulatory pathways for biosimilar drugs being available at the time, tbo-filgrastim is not. Tbo-filgrastim was filed with its own Biologic Drug Application and thus does not share the same indications. Since the time the application for filgrastim-sndz was submitted, the parent molecule, filgrastim was granted an additional indication that filgrastim-sndz does not have.[1,2,9] Sargramostim is the only GM-CSF currently available.[4]

G-CSFs are largely used to prevent and reduce the duration of neutropenia in patients receiving chemotherapy.[59] Several clinical trials have demonstrated efficacy of the G-CSFs for this indication. A systematic review published in 2007 reviewed 17 randomized controlled trials comparing primary prophylactic G-CSF to placebo or untreated controls in adult solid tumor and malignant lymphoma patients. The review reported an overall 46% decrease in the risk of febrile neutropenia, a 45% decrease in infection-related mortality and a 40% decrease in all-cause mortality during the chemotherapy period.[60]

Currently the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO) and European Organization for Research and Treatment of Cancer (EORTC) guidelines recommend CSF prophylaxis in patients whose overall risk of febrile neutropenia is >20%.[9,10,16] Recent retrospective data has reported a potential advantage of pegfilgrastim in reducing the risk of hospitalizations due to febrile neutropenia when compared to filgrastim and sargramostim, while an earlier prospective, randomized trial demonstrated comparable clinical efficacy between filgrastim and pegfilgrastim for the indication of febrile neutropenia.[18-21] The NCCN and the EORTC guidelines currently recommend either G-CSF equally for treatment.[11,13] Moreover, with the lack of clinical studies comparing the efficacy of the G-CSFs and GM-CSF, the ASCO guidelines do not provide recommendations regarding the specific types of products,[12] whereas the NCCN states filgrastim and pegfilgrastim have stronger evidence than sargramostim supporting their use.[11] Additional studies are needed to determine the safety and efficacy differences among the G-CSFs and GM-CSF in febrile neutropenia as well as the other indications.

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References

1. Neupogen® [package insert]. Thousand Oaks (CA): Amgen Inc.; 2015 Mar.
2. Zarxio® [package insert]. Princeton (NJ): Sandoz Inc.; 2015 Mar.
3. Neulasta® [package insert]. Thousand Oaks (CA): Amgen Inc.; 2014 Dec.
4. Leukine® [package insert]. Bridgewater (NJ): Sanofi-Aventis U.S. LLC; 2013 Apr.
5. Granix® [package insert]. North Wales (PA): Teva Pharmaceuticals USA, Inc.; 2014 Dec.
6. Liles WC. Immunomodulators. In: Mandell GL, Bennett JE, Dolin R, editors. Manell, Bennett, & Dolin: Principles and Practice of Infectious Diseases [monograph on the internet]. 7th ed. Philadelphia: Churchill Livingston: 2009 [cited 2011 Apr 19]. Available from: http://www.mdconsult.com/das/book/body/110770361-5/773675061/1259/315.html#4-u1.0-B0-443-06643-4.50042-8--cesec1_1721.
7. Blood Formation, Coagulation, and Thrombosis agents 20.00, Hematopoietic Agents 20.16. In: McEvoy GK, editor: American Hospital Formulary Service. AHFS drug information 2011 [monograph on the internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2011 [cited 2011 Apr 19]. Available from: http://online.statref.com.
8. Medina PJ, Fausel C. Cancer treatment and chemotherapy. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 7th edition. New York (NY): McGraw-Hill; 2008. p. 2085-119.
9. Pappas AL, Hanna, S. *TBO-filgrastim (granix).* Pharmacy Times (2014) Retrieved Aug, 2015, from http://www.pharmacytimes.com/publications/health-system-edition/2014/march2014/tbo-filgrastim-granix.
10. Baehner R. Neutrophil functions other than movement. In: Basow DS (Ed). UpToDate [database on internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Apr 19]. Available from: http://www.utdol.com/utd/index.do.
11. The NCCN Myeloid Growth Factors Clinical Practice Guidelines in Oncology (Version 1.2010). Fort Washington (PA): National Comprehensive Cancer Network, Inc. 2011 [accessed 2011 Apr 17]. Available from: http://www.nccn.org/index.asp.
12. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006 Jul 1;24(19):3187-205.
13. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 2.2011). Fort Washington (PA): National Comprehensive Cancer Network, Inc. 2011 [accessed 2011 Apr 17]. Available from: http://www.nccn.org/index.asp.
14. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011 Jan;47(1):8-32.
15. Micromedex® Healthcare Series [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. [Cited 2014 Sep]. Available from: http://www.thomsonhc.com/.
16. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2014 Sep]. Available from: http://online.factsandcomparisons.com.
17. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2015 [cited: Aug 4 2015]. Available from: http://www.clinicalpharmacology.com.
18. Almenar D, Mayans J, Juan O, Bueno JM, Lopez JI, Frau A, et al. Pegfilgrastim and daily granulocyte colony-stimulating factor: patterns of use and neutropenia-related outcomes in cancer patients in Spain-results of the LEARN Study. Eur J Cancer Care (Engl). 2009 May;18(3):280-6.
19. Weycker D, Malin J, Kim J, Barron R, Edelsberg J, Kartashov A, et al. Risk of hospitalization for neutropenic complications of chemotherapy in patients with primary solid tumors receiving pegfilgrastim or filgrastim prophylaxis: a retrospective cohort study. Clin Ther. 2009 May;31(5):1069-81.
20. Weycker D, Malin J, Barron R, Edelsberg J, Kartashov A, Oster G. Comparative effectiveness of filgrastim, pegfilgrastim, and sargramostim as prophylaxis against hospitalization for neutropenic complications in patients with cancer receiving chemotherapy. Am J Clin Oncol. 2011 Mar 2 [Epub ahead of print]. doi: 10.1097/COC.0b013e31820dc075.

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21. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol. 2002 Feb 1;20(3):727-31.
22. Beveridge RA, Miller JA, Kales AN, et al. A comparison of efficacy of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. Cancer Invest. 1998;16(6):366-73.
23. Beveridge RA, Miller JA, Kales AN, et al. Randomized trial comparing the tolerability of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in cancer patients receiving myelosuppressive chemotherapy. Support Care Cancer. 1997 Jul;5(4):289-98.
24. Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD003189.
25. Heaney ML, Toy EL, Vekeman F, Laliberté F, Dority BL, Perlman D, et al. Comparison of hospitalization risk and associated costs among patients receiving sargramostim, filgrastim, and pegfilgrastim for chemotherapy-induced neutropenia. Cancer. 2009 Oct 15;115(20):4839-48.
26. Nemunaitis J, Rabinowe SN, Singer JW, et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. N Engl J Med. 1991 Jun 20;324(25):1773-8.
27. Lazarus HM, Andersen J, Chen MG, et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for relapsed non-Hodgkin's lymphoma: blood and bone marrow progenitor growth studies. A phase II Eastern Cooperative Oncology Group Trial. Blood. 1991 Aug 1;78(3):830-7.
28. Rabinowe SN, Neuberg D, Bierman PJ, et al. Long-term follow-up of a phase III study of recombinant human granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid malignancies. Blood. 1993 Apr 1;81(7):1903-8.
29. Nemunaitis J, Rosenfeld CS, Ash R, et al. Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. Bone Marrow Transplant. 1995 Jun;15(6):949-54.
30. Bernini JC, Wooley R, Buchanan GR. Low-dose recombinant human granulocyte colony-stimulating factor therapy in children with symptomatic chronic idiopathic neutropenia. J Pediatr. 1996 Oct;129(4):551-8.
31. Welte K, Zeidler C, Reiter A, et al. Differential effects of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor in children with severe congenital neutropenia. Blood. 1990 Mar 1;75(5):1056-63.
32. Grigg A, Solal-Celigny P, Hoskin P, et al. Open-label, randomized study of pegfilgrastim vs daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma. Leuk Lymphoma. 2003 Sep;44(9):1503-8.
33. Holmes FA, Jones SE, O'Shaughnessy J, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. Ann Oncol. 2002 Jun;13(6):903-9.
34. Green MD, Koelbl H, Baselga J, et al. VA randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol. 2003 Jan;14(1):29-35.
35. Vose JM, Crump M, Lazarus H, et al. Randomized, multicenter, open-label study of pegfilgrastim compared to daily filgrastim after chemotherapy for lymphoma. J Clin Oncol. 2003 Feb 1;21(3):514-9.
36. Staber PB, Holub R, Linkesch W, Schmidt H, Neumeister P. Fixed-dose single administration of Pegfilgrastim vs daily Filgrastim in patients with hematological malignancies undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 2005 May;35(9):889-93.
37. Milkovich G, Moleski RJ, Reitan JF, et al. Comparative safety of filgrastim versus sargramostim in patients receiving myelosuppressive chemotherapy. Pharmacotherapy. 2000 Dec;20(12):1432-40.
38. del Giglio A, Eniu A, Ganea-Motan D, Topuzov E, Lubenau H. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile

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neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer. 2008 Nov 12;8:332. doi: 10.1186/1471-2407-8-332.
39. Engert A, Griskevicius L, Zyuzgin Y, Lubenau H, del Giglio A. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. Leuk Lymphoma. 2009 Mar;50(3):374-9. doi: 10.1080/10428190902756081.
40. Gatzemeier U, Ciuleanu T, Dediu M, Ganea-Motan E, Lubenau H, Del Giglio A. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. J Thorac Oncol. 2009 Jun;4(6):736-40. doi: 10.1097/JTO.0b013e3181a52964.
41. Weisdorf DJ, Verfaillie CM, Davies SM, et al. Hematopoietic growth factors for graft failure after bone marrow transplantation: a randomized trial of granulocyte-macrophage colony-stimulating factor (GM-CSF) vs sequential GM-CSF plus granulocyte-CSF. Blood. 1995 Jun 15;85(12):3452-6.
42. Nemunaitis J, Singer JW, Buckner CD, et al. Use of recombinant human granulocyte-macrophage colony-stimulating factor in graft failure after bone marrow transplantation. Blood. 1990 Jul 1;76(1):245-53.
43. Putkonen M, Rauhala A, Pelliniemi TT, Remes K. Single-dose pegfilgrastim is comparable to daily filgrastim in mobilizing peripheral blood stem cells: a case-matched study in patients with lymphoproliferative malignancies. Ann Hematol. 2009 Jul;88(7):673-80.
44. Martino M, Pratico` G, Messina G, et al. Pegfilgrastim compared to filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. Eur J Haematol. 2006 Nov;77(5):410-5.
45. Martino M, Pratico` G, Messina G, et al. Pegfilgrastim compared to filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. Eur J Haematol. 2006 Nov;77(5):410-5.
46. Castagna L, Bramanti S, Levis A, Michieli MG, Anastasia A, Mazza R, et al. Pegfilgrastim vs filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. Ann Oncol. 2010 Jul;21(7):1482-5.
47. Mathew S, Adel N, Rice RD, Panageas K, Duck ET, Comenzo RL, et al. Retrospective comparison of the effects of filgrastim and pegfilgrastim on the pace of engraftment in auto-SCT patients. Bone Marrow Transplant. 2010 Oct;45(10):1522-7.
48. Samaras P, Buset EM, Siciliano RD, Haile SR, Petrausch U, Mischo A, et al. Equivalence of pegfilgrastim and filgrastim in lymphoma patients treated with BEAM followed by autologous stem cell transplantation. Oncology. 2010;79(1-2):93-7.
49. Samaras P, Blickenstorfer M, Siciliano RD, Haile SR, Buset EM, Petrausch U, et al. Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with melphalan 200 and auto-SCT compared to filgrastim. Ann Hematol. 2011 Jan;90(1):89-94.
50. Jansen J, Thompson EM, Hanks S, et al. Hematopoietic growth factor after autologous peripheral blood transplantation: comparison of G-CSF and GM-CSF. Bone Marrow Transplant. 1999 Jun;23(12):1251-6.
51. Stone RM, Berg DT, George SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. N Engl J Med. 1995 Jun 22;332(25):1671-7.
52. Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (> 55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood. 1995 Jul 15;86(2):457-62.
53. Büchner T, Hiddemann W, Koenigsmann M, et al. Recombinant human granulocyte-macrophage colony-stimulating factor after chemotherapy in patients with acute myeloid leukemia at higher age or after relapse. Blood. 1991 Sep 1;78(5):1190-7.
54. Pagliuca A, Carrington PA, Pettengell R, Rule S, Keidan J, Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Guidelines on the use of colony-stimulating factors in hematological malignancies. Br J Haematol. 2003 Oct;123(1):22-33.

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55. British Committee for Standards in Haematology, Milligan DW, Grimwade D, Cullis JO, Bond L, Swirsky D, Craddock C, Kell J, Homewood J, Campbell K, McGinley S, Wheatley K, Jackson G. Guidelines on the management of acute myeloid leukemia in adults. Br J Haematol. 2006 Nov;135(4):450-74.
56. The NCCN. Myelodysplastic Syndromes Clinical Practice Guidelines in Oncology (Version 2.2011). Fort Washington (PA): National Comprehensive Cancer Network, Inc. 2011 [accessed 2011 Apr 17]. Available from: http://www.nccn.org.
57. Bowen D, Culligan D, Jowitt S, Kelsey S, Mufti G, Oscier D, Parker J; UK MDS Guidelines Group. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol. 2003 Jan;120(2):187-200.
58. Stull DM. Colony-stimulating factors: beyond the effects on hematopoiesis. Am J Health Syst Pharm. 2002 Apr 1;59(7 Suppl 2):S12-20.
59. Sieff CA. Introduction to recombinant hematopoietic growth factors. In: Basow DS (Ed). UpToDate [database on internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Apr 17]. Available from: http://www.utdol.com/utd/index.do.
60. Kuderer NM; Dale DC; Crawford J; Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol. 2007 Jul 20;25(21):3158-67.

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